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A MATHEMATICAL MODEL OF THE HUMAN EXTERNAL RESPIRATORY SYSTEM

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SUMMARY

This study examines the thesis that a part of the human physiological system can be simulated by a suitably constructed mathematical model. The model employed derives from a class of mathematical programming methods that were originally developed for representing complex military and industrial activities and have recently been used to represent involved chemical equilibria.

The motivation for this research is the long-range view that a successful mathematical simulation of the human system or of human subsystems would provide an important tool for biological investigations. A sufficiently complex mathematical model—that is, a model that embodies sufficient chemical and biological detail to represent a whole, functioning human system or subsystem—could be used to explore biological hypotheses, environmental stress reactions, and interplay of dependent subsystems, and could serve as a pedagogical tool or even as an aid to medical diagnosis.

Of course, the foregoing long-range view is an ultimate goal. For the moment, only the techniques, concepts, and characteristics of such a mathematical model are being explored.

This paper presents the results of a simulation of the external respiratory function. Respiration, and the consequent gas exchanges at the lung surfaces, involves many chemical reactions and a transformation of venous blood into arterial blood. This activity was chosen as a test case to explore the feasibility of constructing a mathematical model of a human subsystem.

Basing their work on the known physiological and chemical aspects of this subsystem, the authors have constructed a mathematical model that, when solved, yields values describing the major phenomena of the subsystem. The values of some thirty different molecular species as determined by the model are in excellent agreement with observed values.

In the present form of the model, emphasis was placed on the chemistry and thermodynamics of the subsystem rather than on the physical dynamics, such as flow and mixing. These time-phased phenomena are expressed only implicitly at this stage. In spite of these and other approximations, this exercise appears to demonstrate that the mathematical art is now capable of representing such systems having large and complex sets of functionally interrelated variables, and that there is reason to be optimistic about the possibilities of representing other more complicated human subsystems and interconnecting them.

FOREWORD

Traditionally, the Doctor of Medicine has been trained first in the basic sciences of anatomy, biochemistry, physiology, pathology, and pharmacology. Subsequently, in his clinical years he has been trained to integrate and relate the knowledge obtained in these basic sciences of medicine as they apply to the individual patient.

Since the turn of the century, the accumulation of knowledge — not only in the clinical fields but also in the basic sciences — has become so vast that there has necessarily developed a fragmentation into many specialties and subspecialties.

The human body may be considered in one aspect as perhaps the most complex chemical factory ever devised. It is a dynamic chemical factory in which there are no absolute values. The recent introduction of isotope techniques into medicine has re-emphasized the dynamic state of the human body.

Recognizing the dangers inherent in oversimplification, we might nevertheless say that in medicine we are dealing functionally with highly complex systems of oxidation-reduction reactions and with control mechanisms affecting the varying rates of these reactions. Of the hundreds of parameters measured in medicine, we are, in fact, measuring indices of rates of conversions at a given time. The availability of

energy to control these rates may be a critical factor in such normal processes as growth and aging — and in the variations from these normal processes, which we may view as diseased states or pathological conditions.

New approaches must be undertaken to assist in viewing the human body as a whole. These approaches must be applicable to the integration and evaluation of information and of a very large number of parameters that have been accumulated but not necessarily interrelated in the hundreds of special fields in which research has been undertaken in the study of the human body.

It now appears feasible to use advanced techniques of mathematical programming and computers as one means of gaining greater insight into the over-all complexities of the functioning of the human body in relation to its anatomical structure. The present trial study has demonstrated the feasibility of this approach as applied to oxygen utilization.

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ACKNOWLEDGMENTS

The authors wish especially to emphasize the important role of the United States Air Force in making possible the present research on a human physiological system. Starting in 1949, the Air Force (with support from the Army and Navy) contracted with the National Academy of Sciences — National Research Council to gather, and to compile in handbook form, basic established data in the biological and medical sciences. This work was administered under the direction of the Aero Medical Laboratory, Wright Air Development Center (WADC). A number of outstanding publications have resulted from this Contract. Two of these were heavily relied on to accomplish the mathematical representation developed in this study: Standard Values in Blood, Air Force Technical Report No. 6039, July, 1951, and Handbook of Biological Data, WADC Technical Report 56-273, Dayton, Ohio, October, 1956. In addition to containing extensive and reliable data, these publications are unique in their rigorous presentation of the data on a comparable and representative basis. This rigor is essential for the construction and validation of mathematical models.

Another significant Air Force research contribution that was a most important aid in the RAND work is the publication, Handbook of Respiratory Physiology, compiled under the aegis of the USAF School of Aviation Medicine, Air University, in 1954. This is a scientific treatise on the various aspects

of human respiration, with sections prepared by outstanding experts in the field from within and from without the Air Force.

The contributions of Dr. Crawford F. Sams of the University of California to the planning and execution of this research were made possible by the support of the Office of Civil and Defense Mobilization (OCDM) through the Civil Defense Research Project at the University. The cooperation of the University of California and OCDM in this arrangement is gratefully acknowledged.

CONTENTS

I. THE GENERAL OBJECTIVE

> The only way of real advance in biology lies in taking as our starting point, not the separated parts of an organism and its environment, but the whole organism in its actual relation to environment, and defining the parts and activities in this whole in terms implying their existing relationships to the other parts and activities. — J. B. S. Haldane

Haldane's formulation[1] of the prerequisite for important advances in biology was made by that eminent British biologist thirty-seven years ago. Until very recently, its implementation had seemed well beyond the capabilities of human accomplishment. This is not to imply that biologists, physiologists, and medical researchers have failed to develop a knowledge of the micromechanisms of the reactions occurring in the separated parts of organisms. On the contrary, these scientists, working in many countries, have amassed a remarkable amount of data relating to reactions occurring in organisms and parts of organisms ranging from the single cell to complicated multifunctioning organs of the human system. The problem of interrelating and synthesizing these multitudes of dependent reactions into entire systems or even into subsystems representative of the organism has, however, remained unsolved.

The diagnostician has resorted to intuition in attempting to synthesize in his mind the results of tests of isolated functions in terms of the subsystem of particular interest.

Physiologists have had no suitable means for relating a new understanding of the functioning of a part of an organism to larger parts or to the system as a whole. Chemists developing new drugs have been handicapped in obtaining an appreciation of the possible effects and side effects of these drugs in vivo.

The coming nuclear and space age presents an especially difficult challenge to the biological sciences and to the medical arts. The stresses that may be placed on organisms by the completely new and stringent environments associated with these technologies are largely unknown. An understanding of the effects of these environments on the whole organism, especially on the human system, will be difficult and slow if not impossible to obtain within the present state of the biological arts and sciences. This is partly because of our lack of knowledge of individual biological phenomena and partly because of the present lack of a technique allowing the integration of a very large number of environmental effects, which may operate primarily through a part, on the whole system. We shall not try to decide in advance which lack is more important. However, mathematical techniques and computing facilities are now becoming available for integrating increasingly complicated sets of components. It is felt that these techniques should be pushed to the biological or mathematical limit — whichever comes first — in the hope of constructing mathematical models for increasingly large

portions of the human system.

The idea of building mathematical models of biological systems is, of course, not new. Many investigators have explored the possibilities in the past and the field is attracting increasing attention at present. The names of Lotka, Rashevsky, Henderson, Michaelis among others come to mind as early investigators who proposed mathematical models of biological systems or who pioneered in the quantification of parts of such systems. Present interest in the subject is attested by the devotion of two complete issues of Reviews of Modern Physics (January and April 1959) to papers dealing with the quantification of biological processes. Weinrauch and Hetherington have recently reviewed the increasing activity in the application of electronic computers to the study of biological problems. (J.A.M.A. January 17, 1959 pp. 120–125.)

II. ON THE FEASIBILITY OF A MATHEMATICAL MODEL OF THE HUMAN SYSTEM

In considering the foregoing situation, the authors believed that the difficult biological problem of relating the parts to the whole, and the whole to the environment, might be well served by employing some of the newer mathematical programming techniques that have been applied successfully in representing other systems of comparable complexity and number of components. Thus, linear and nonlinear programming models have been successfully constructed to schedule the activities of vast industrial and military enterprises.

The general approach is to view the collection of organs of the body — the heart, lungs, liver, skin, arteries, veins, etc. — as an interrelated and interdependent physical set of subsystems each of which performs a well-defined function or activity such as the pumping activity of the heart. For a particular organ, the level of activity must be consistent with certain inputs from other organs and must not exceed the given capacity of the organ — for example, the pumping activity of the heart is limited by its physical size and the availability of oxygen to heart muscles, and also by the volume of blood available from the veins. The result of a given level of activity is certain outputs to other organs.

If it were valid to assume that a change in the activity level of an organ results in a proportional change in its inputs and outputs, then the resulting mathematical model would

be of the pure linear-programming type. It is immediately evident, however, that gross functions such as the respiratory function or the liver function do not remotely satisfy the condition of proportional inputs and outputs. Indeed, these systems can function under an almost endless variety of complicated inputs producing a correspondingly complicated variety of outputs. Nevertheless, if we broaden our definition of activity to include the forming of various chemical species within some gross function, then these more elementary functions in most respects satisfy such an assumption of proportionality, the well-known chemical law of combining proportions. In other respects, these elementary functions are quite different. Thus the amounts of various substances formed when venous blood and air come in contact through the alveolar surfaces of the lungs must also satisfy known laws for chemical equilibria. In other cases, such as blood circulation, basic relationships drawn from the science of hydrodynamics play an important role.

Thus a human-system model, while possessing many characteristics of those used successfully to program human group activities, has other characteristics that result in a more complex structure. One aspect of the mathematical system is clear. It must involve many variables, representing levels of activity of certain organs and rates of flow of many substances, and these must satisfy a large number of

equations and inequalities expressing the limitations of capacity and availability from other organs and sources.

It is the authors' belief that the successful development of mathematical models capable of handling such a multitude of variables, and especially the more recent mating of these types of models with chemical thermodynamics, provide encouragement that the complexities of physiology may be amenable to mathematical representation and solution.

Developing a complete and integrated human-system representation is quite a large order. In the first place, the size of medical libraries alone attests to the large volume of special cases that such a model would be required in some sense to interpret. One might nevertheless argue that, with luck and several years of effort by a large number of qualified specialists, it might be possible to handle the task if it were not for one outstanding fact — the great gaps in our knowledge of the human system. To cite one obvious example, we know the brain plays a major role in the control of the physical processes of the body, but the exact functional relationships that define the control can at best only be hypothesized.

How then can one presume to build a mathematical model of the whole human system? The only way of doing this is, as in all science, through the combined use of fact and hypothesis. Thus, in areas where the underlying mechanism is unknown, it is generally true that either X's or Y's hypothesis

can be used to fill the gap. Incorporation of a hypothesis into the model may provide a useful way of testing the hypothesis by comparing observations made under a variety of conditions with those predicted by the model under similar conditions.

It is the opinion of the authors that a mathematical model of the human system can be built largely on the functional relationships derived from basic physical and chemical laws. Such a model is not limited by the range of empirical observational data. Rather, the mathematical system permits the exploration of wide ranges of situations that may represent extremes of environmental or pathological conditions. Even if at first the results of such mathematical explorations frequently do not correspond to reality, much useful knowledge can be obtained in determining the reasons for the lack of correspondence.

The remainder of this paper describes the results of applying these techniques to the human respiratory system. Other human subsystems should also be amenable to representation by the techniques described. Possibly in ascending order of difficulty, these might be the following:

Total metabolic system, including digestion, nutrition, and excretory functions.

Synthesis, storage, and conversion system, including functions of the liver, blood-forming tissue, and muscles

Hormonal regulatory system.

Central and peripheral nervous system.

Mechano—skeletal response system.

It is quite possible, of course, that — as the research results unfold — this ordering may be changed or different groupings of components may prove more expedient.

It is not known whether the simultaneous operation of models of several human subsystems in detail would be beyond the capabilities of currently available computing machinery. If each should turn out to be no bigger than the respiratory model, there would be no problem. This, however, seems unlikely. Nevertheless, because of some unique characteristics of the chemical systems represented, and their thermodynamics, and the flexibility of the model, it appears to be possible to employ some tricks that may allow an interesting number of subsystems to be operated concurrently with present equipment. Moreover, in many cases the additive qualities of the chemistry can permit parts or all of a subsystem to be aggregated, and yet allow the essential relationships with the rest of the subsystem or with other subsystems to be maintained. This phenomenon is something like looking at the human system with a microscope. A small field that is being examined can be seen in great detail, while the rest of the system, still operating, is involved only grossly.

III. A REVIEW OF THE PHYSIOLOGY AND CHEMISTRY OF THE EXTERNAL RESPIRATORY SYSTEM

To confirm the belief that complex physiological systems can be represented by mathematical programming techniques, the authors selected one important subsystem of the human organism—the external respiratory system—as an exercise.* This subsystem includes the functions of breathing, the transfer of gases to and from the blood, the complex oxygen and carbon-dioxide transport in the arterial and venous blood, the reactions between blood plasma and red cells, the reactions within the red cells, the transfer of oxygen and carbon dioxide with the body tissues, and the flow of blood through heart action. An important reason for selecting this subsystem for mathematical study is that it has been extensively investigated and a large amount of quantitative data are available for validating a model.

Figure 1 illustrates in a schematic fashion the gross physiological aspects of the external respiratory system in man. The ultimate purpose of this system is to provide oxygen from the atmosphere to oxidize carbonaceous food, thereby generating heat and supplying energy for performing work, and to return to the atmosphere the CO_2 (and some of the water) that is formed by these reactions occurring in the cells of

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*The internal respiratory system relates to the metabolic processes occurring at the cellular level. These processes are not represented explicitly in the present exercise.

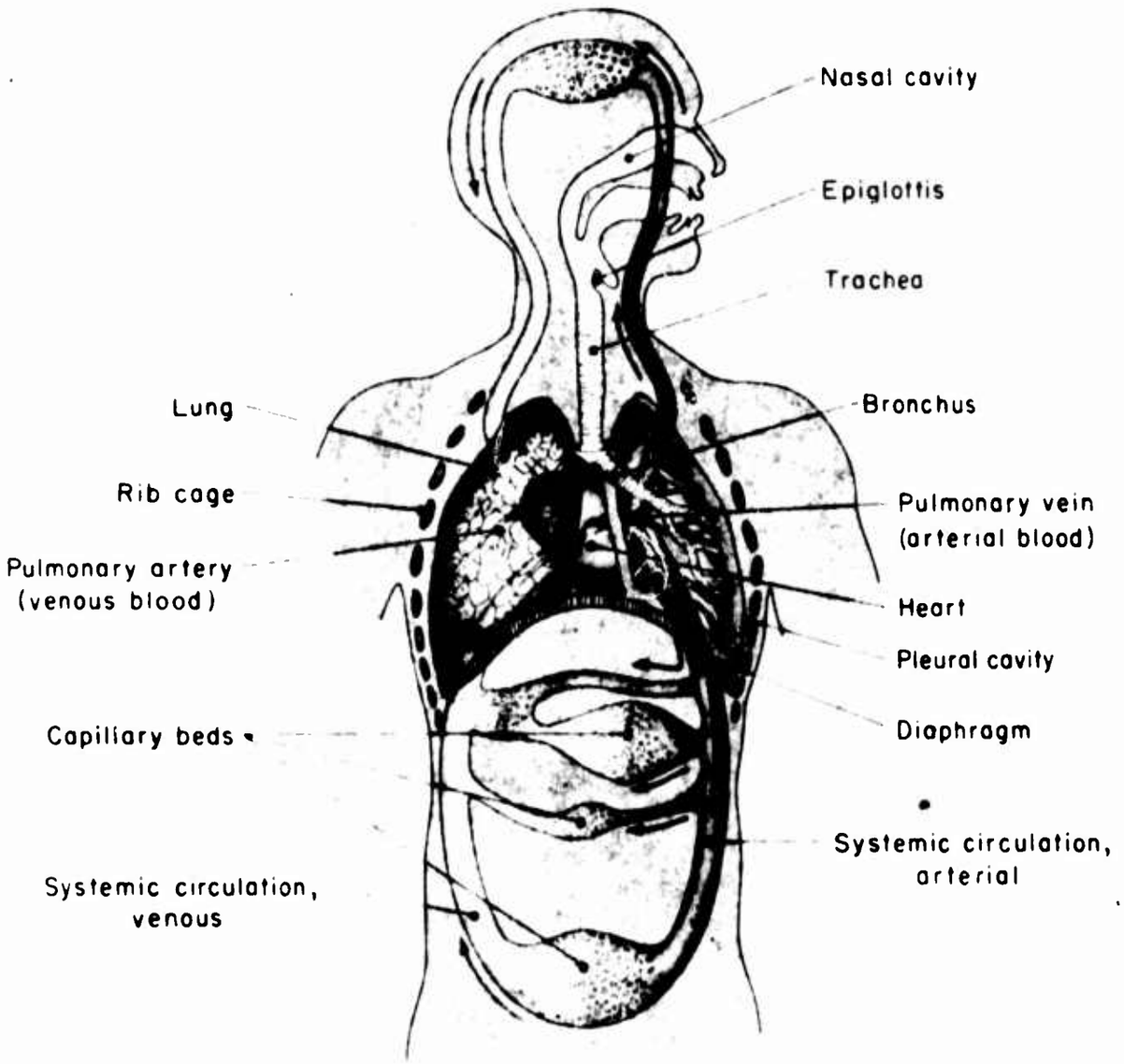

Fig. 1 — Gross physiological aspects of the human respiratory system (schematic)

body tissues. The exchange of gases between the blood and the external atmosphere takes place in the lungs by transfer across the extremely thin walls of the capillaries and the pulmonary alveoli.

The air passages to and from these exchange membranes include the nasal cavities, the pharynx, larynx, trachea, bronchi, and bronchioles. The lung tissue proper contains an immense number of irregularly shaped air spaces, called alveolar sacs. The terminal twigs of the bronchial tree open into these alveolar sacs; see Fig. 2. The number of pulmonary alveoli in the lungs of man has been estimated at 7.5×10^8. The tremendous surface area presented by the alveoli for gas exchange results in close-to-equilibrium conditions between arterial blood and sac-gas composition except under transient stress conditions.

The lungs play a passive role in inspiration and expiration. Their change in volume during this cycle is brought about through change in the capacity of the thoracic cavity. The change in capacity of this cavity is caused by the descent and ascent of the diaphragm, and by the movement of the rib cage.

Only about one-half liter, or one-tenth of the total air capacity of the lungs, is inspired and expired during ordinary quiet breathing. This is called the tidal air. Even after the most forceful expiration, from 1000 to 1500 cc of air remains in the lungs. The space enclosed by the bronchi,

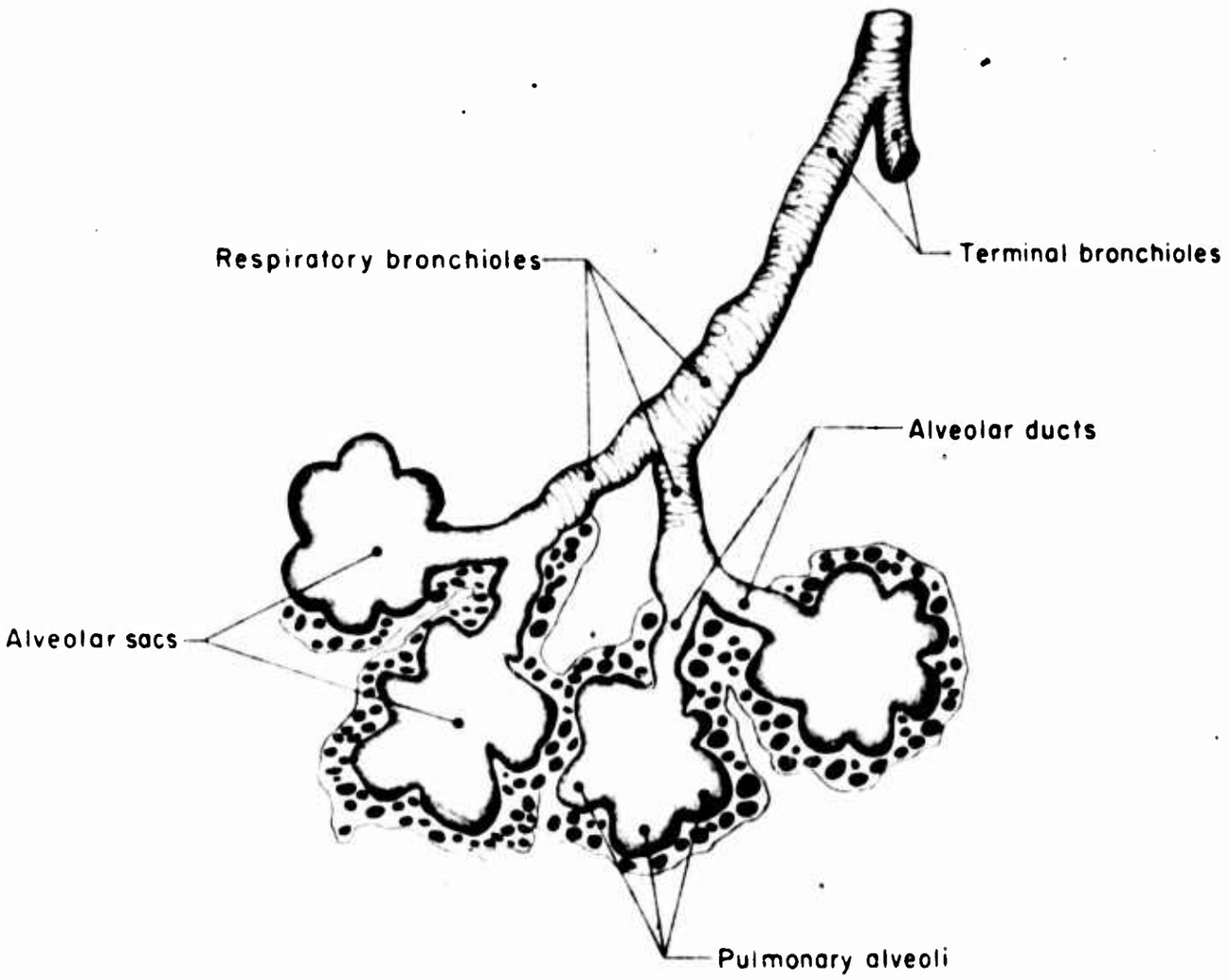

Fig. 2 — Diagrammatic representation of a respiratory unit (Ref. 2)

bronchioles, trachea, larynx, pharynx, and nasal cavities is called the dead-air space. It has a capacity of about 150 cc. The air in the air sacs is termed the alveolar air. Various techniques have been developed for measuring or estimating the composition of this sac air, which is in equilibrium with arterial blood and which is different from the external atmosphere.

The foregoing characteristics of the lungs, especially the small tidal volume in respect to total capacity and in respect to the large residual volume, permit the lungs to accomplish the remarkable function of damping out the large fluctuations of sac-air composition that otherwise, during the intermittent inspiration-expiration cycle, would subject the flowing blood to large surges of oxygen (and alternately of carbon dioxide). To a first approximation, this lung characteristic permits the breathing mechanisms to be represented as a large volume of air of sac composition in equilibrium with the blood.

Actually, the breathing mechanism and changes of air composition from atmosphere to lung sac are quite complex in detail. The blood gives off carbon dioxide (and usually water) to the lung sacs and picks up oxygen. Thus, the air leaving the sacs is of a different composition from the incoming air. On top of this change, there are other factors such as diffusion, mixing, the dead-air space, the alternate

inspiration—expiration cycle, and the blood—flow rate that all affect the composition of sac air in relation to atmospheric air.

One's breathing rate can be controlled voluntarily within limits, but it is essentially an involuntary act controlled automatically by the rhythmical discharge of impulses from a group of nerve cells in the medulla oblongata of the brain. This respiration center is influenced largely by changes of carbon—dioxide concentration in the blood. Changes in oxygen concentration can also influence the breathing rate, but this is thought to be an indirect influence through chemoreceptors lying close to the heart. These chemoreceptors also appear to be influenced within limits by hydrogen—ion and carbon—dioxide concentration, in addition to affecting heart—action and blood—flow rates and indirectly influencing breathing.

The gaseous exchanges between the blood and the tissues are the reverse of those taking place in the lungs. The oxygen concentration is lower and the carbon—dioxide concentration is higher in the tissues than in arterial blood. Therefore, in passing through the systemic capillaries, the blood gives up oxygen and absorbs carbon dioxide. The composition of the blood returning to the lungs varies, depending on the part of the body it has served. There is also some admixture of arterial blood with the venous as it enters the lungs. As a result, the blood entering the lungs — which is

called mixed-venous blood — is higher in oxygen and lower in carbon dioxide than the most degraded venous blood, such as that coming from an extremity and sampled there.

The chemical phenomena of the external respiratory system in which we are especially interested may be represented schematically as in Fig. 5. Here the system is considered as consisting of three compartments, corresponding to the lung sacs, the blood plasma, and the red blood cells. Following first the path of oxygen from the lung sacs, we note that inasmuch as the concentration of oxygen dissolved in mixed-venous plasma is lower than that dictated by the partial pressure of oxygen in the lung sacs, oxygen transfers from the sacs to plasma, increasing its concentration there and in red-cell solution. This increased oxygen concentration causes the reduced hemoglobin in the red cells to combine with oxygen until a new equilibrium is reached at the higher oxygen concentration. Hemoglobin accounts for the large percentage of oxygen carried by the blood; however, as is also true of carbon dioxide, its solution in plasma and red cells serves as the important pathway in and out of the blood.

Conversely to the case of oxygen, the concentration of carbon dioxide is higher in mixed-venous plasma than that dictated by the partial pressure of carbon dioxide in the lung sacs, so carbon dioxide transfers from the plasma to the sacs until a new equilibrium is reached at a lower carbon-dioxide concentration. But carbon dioxide is stored by the blood in

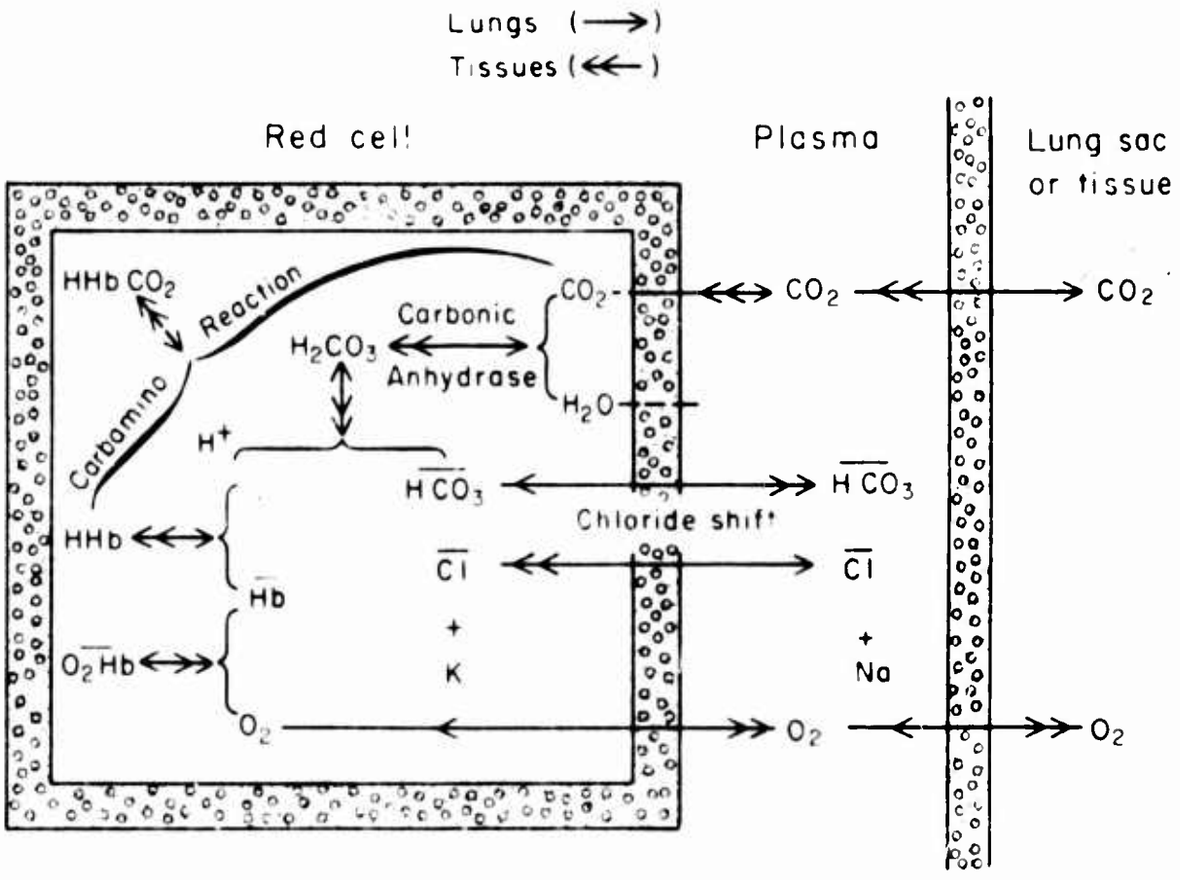

Fig. 3 — Chemical aspects of the external respiratory system (Ref. 3)

both plasma and red cells largely as bicarbonate ion (and in association with reduced hemoglobin in the carbamino form). As the carbon-dioxide concentration is reduced, the bicarbonate-ion concentration is also reduced. This reaction in the red cells is catalyzed by the enzyme carbonic anhydrase. As the bicarbonate concentration in the red cells decreases, an important reaction called the "chloride shift" takes place across the cell membrane; in this reaction, bicarbonate ion from the plasma transfers to the red cells, and chloride ion from the red cells transfers to the plasma. The reverse of this shift occurs at the tissues when carbon-dioxide concentration increases in the blood. Here, bicarbonate ion formed in the red cells shifts to the plasma and chloride ion shifts to the red cells. This shift results in an increase in the carbon-dioxide carrying power of the blood. The remarkable ion-selective characteristics of the red-cell membrane and the resulting Gibbs-Donnan equilibrium make this important shift possible.

As mentioned, carbon dioxide is also carried by hemoglobin. This hemoglobin-linked carbon dioxide, while representing only a small part of the total carried by the blood, provides a significant part of the carbon dioxide transferred from tissues to lung sacs.

The physiology and the chemistry of the external respiratory system are, of course, much more complex in detail than

could possibly be indicated in this brief description.* This introduction, however, should provide the background necessary for an understanding of the mathematical representation of the more important features of this system.

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*An excellent detailed description of the external respiratory system is contained in Ref. 4.

IV. A MATHEMATICAL MODEL OF THE CHEMISTRY OF THE EXTERNAL RESPIRATORY SYSTEM

DESCRIPTION OF THE MODEL

From the physiological data available and the working of the respiratory system as outlined above in Sec. III, a mathematical model was set up to represent the more important of the known interrelated physiological functions and chemical reactions involved in the human respiratory system. Actually, two models were formulated. Model I uses a simplified concept of the hemoglobin molecule, but otherwise is sufficiently detailed for the present purpose. Model II, described in Appendix D, is based on Linus Pauling's theory of the complex hemoglobin molecular structure.

Figure 4, which is a schematic illustration of the external respiratory system, demonstrates the relationship of the inputs and outputs of the mathematical model to the actual system. The a's and v's in the figure refer to the input "elements" coming to the lungs in unit time from mixed-venous blood and from the air. The x's refer to the resulting numerous molecular species in the arterial blood and in the air of the lung sacs as determined by the solution of the mathematical model. At the present stage, the cell outputs are introduced into the model in terms of the composition of the mixed-venous blood.

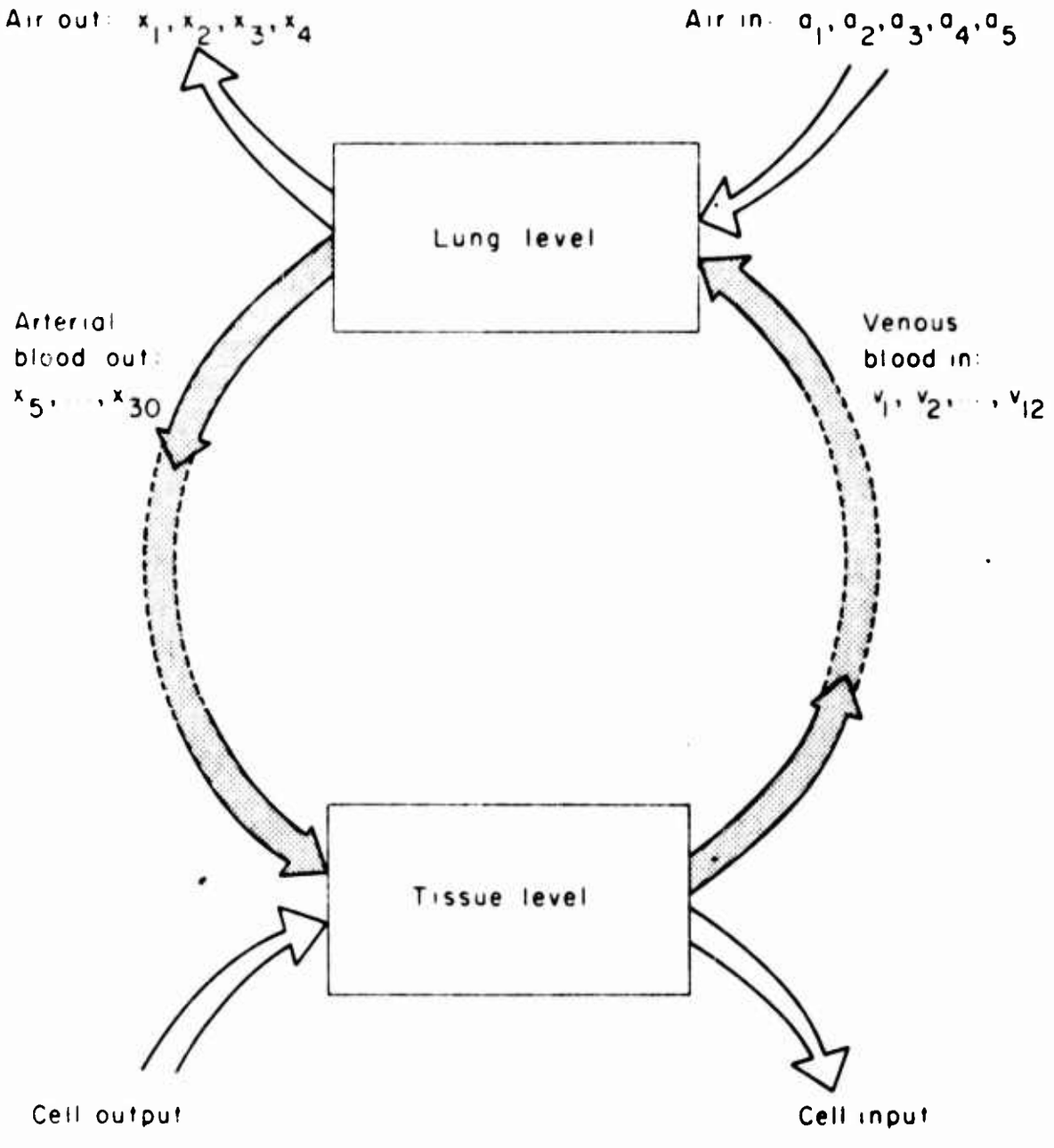

Fig. 4 — The relationship of the inputs and outputs of Model I to the respiratory system

Model I was constructed to provide an accounting of the mass of all of the "elements" involved. The concentration of each of the molecular species (dissolved compounds, gases, ions) was established in terms of its mole fraction. Since the equilibrium constants for the many reactions were available, it was possible to interrelate, within the model, the mutual effects of changes in concentration of any of the species. Further, from the equilibrium constants and mole fractions, it was possible, on the assumption of ideal solution behavior in the dilute solutions involved, to establish the thermodynamics of the system within the model.

Some previous studies at RAND[5] provided a technique for the introduction of these energetics of the system into the computational model in an efficient manner. This method makes use of the Gibbs' chemical-potential concept with the minimization of total potential energy of the system defining equilibrium, rather than use of the equilibirum constants and their more conventional relation to free energy. The two concepts are mathematically equivalent. In the first part of Appendix A, the interested reader will find a review of the basic chemical and thermodynamic concepts employed in the present development.

The model constructed to represent this system is shown in Table 1. Briefly, the input data of the model consist of given quantities of the "elements" of mixed-venous blood and air, shown on the left in the table. The output data are the

Table 1

MODEL I. THE EXTERNAL RESPIRATORY SYSTEM

Input "Elements" (moles)				Output Composition by Molecular Species																													
	Source			I. Air Out				II. Arterial Plasma												III. Red Cells													
"Element"	Air	V. Blood	Total $b_i = a_i + v_i$	O_2	CO_2	N_2	H_2O	O_2	CO_2	N_2	H^+	OH^-	Cl^-	Na^+	H_2O	HCO_3^-	H_2CO_3	$CO_3^=$	HP_p^- (a)	O_2	CO_2	N_2	H^+	OH^-	Cl^-	K^+	H_2O	HCO_3^-	H_2CO_3	$CO_3^=$	HBl^- (b)	$HBlO_2$ (b)	HP_r^- (c)
								Unknown Quantities x_j (moles)																									
				$x_1 \cdots x_4$				$x_5 x_6 \cdots x_{16}$												$x_{17} \cdots x_{30}$													
								Detached Coefficient Values a_{ij}																									
O_2	a_1	v_1	b_1	1				1												1												1	
CO_2	a_2	v_2	b_2		1				1							1	1	1			1							1	1	1			
N_2	a_3	v_3	b_3			1				1												1											
H^+	a_4	v_4	b_4				1				1				1		1	−1					1				1		1	−1			
OH^-	a_5	v_5	b_5				1					1			1	1	1	1						1			1	1	1	1			
Cl^-	$a_6 = 0$	v_6	b_6										1												1								
Na^+	$a_7 = 0$	v_7	b_7											1																			
K^+	$a_8 = 0$	v_8	b_8																							1							
HBl^- (b)	$a_9 = 0$	v_9	b_9																												1	1	
HP_p^- (a)	$a_{10} = 0$	v_{10}	b_{10}																1														
HP_r^- (c)	$a_{11} = 0$	v_{11}	b_{11}																														1
Charge z	$a_{12} = 0$	$v_{12} = 0$	$b_{12} = 0$	•							+1	−1	−1	+1		−1		−2	−1														
Free-energy values c_j (d)				$c_1 \cdots c_4$				$c_5 c_6 \cdots c_{16}$												$c_{17} \cdots c_{30}$													

[a] HP_p^- = Misc. Protein in Plasma.

[b] HBl = 1/4 Hemoglobin Molecule.

[c] HP_r^- = Misc. Protein in Red Cells.

[d] All values $c_j = 0$ except $c_1 = -10.89$; $c_2 = -7.69$; $c_3 = -11.49$; $c_{12} = c_{24} = -39.23$; $c_4 = -36.44$; $c_{13} = c_{25} = -21.20$; $c_{29} = -16.23$; $c_{15} = c_{27} = 6.25$.

evaluations of the quantities x_j representing the amounts of various molecular species found in three compartments representing lung-sac air, blood plasma, and red cells. The numbers appearing in the various columns for the individual molecular species characterize the species and are therefore independent of their quantity. In greater detail, the model consists of the following portions:

1. An "Input Section" consisting of given amounts v_i of essential "elements" "i" of the blood corresponding to typical mixed-venous blood values (measured in moles), plus amounts a_i of fresh air "elements" "i," giving total inputs $b_i = a_i + v_i$. (For simple chemical reactions, the "elements" could be defined as the atomic types composing the molecular species. It was more convenient for the present application to compose the various possible molecular species appearing in blood from a set of "elements" consisting of either atoms or "groups of atoms in fixed proportions," such as H^+ or OH^-.)

2. Compartment I, labeled "Air Out," with columns corresponding to different species of lung-sac gases in equilibrium with the arterial plasma and red cells.

3. Compartment II, labeled "Arterial Plasma," with columns corresponding to chemical species appropriate to the arterial plasma. When the model is "solved," the corresponding values are the equilibrium amounts (in moles) of the species in lung sacs, plasma, and red cells.

4. Compartment III, labeled "Red Cells," with columns corresponding to chemical species contained in red cells. As noted earlier, Model I uses a simplified structure. A more complete theory is contained in Model II; see Appendix D.

The mathematical problem for Model I is the following:

For given values b_i ($i = 1, 2, \ldots, 12$), and for the detached coefficient values a_{ij} given in Table 1, determine equilibrium amounts x_j ($j = 1, 2, \ldots, 30$), and minimum free energy z defined by

$$z = \sum_{I} x_j \left[c_j + \ln(x_j/\bar{x}_I)\right] + \sum_{II} x_j \left[c_j + \ln(x_j/\bar{x}_{II})\right] + \sum_{III} x_j \left[c_j + \ln(x_j/\bar{x}_{III})\right],$$

where $\sum_k$ denotes the sum over all species j in compartment k (k = I, II, or III), c_j is proportional to the free energy per mole of the jth species, $\bar{x}_k = \sum_k x_j$ is the total moles in compartment k, and ln means natural logarithm, subject to the constraints

$$x_j \geq 0 \quad (j = 1, 2, \ldots, 30),$$

$$b_i = \sum_{j=1}^{30} a_{ij} x_j \quad (i = 1, 2, \ldots, 12).$$

Thus, the computational problem as presented in the model is to determine the amounts of each of the chemical species present in the lung sacs, in arterial plasma, and in red cells at equilibrium.

In the past, the determination of equilibrium compositions of such large chemical systems involved computational problems that have been tedious and time-consuming; they have often been "solved" by assuming certain species to be dominant in the final solution.[6][7] In recent years, however, several conceptual and computational developments plus the availability of large electronic computing machines have made it feasible to attempt the solution of such large-scale problems repeatedly, and under any desired variation of the basic inputs into the system.[5]

THE FREE-ENERGY FUNCTION

The method here used for solving the system is described in detail in Ref. 5. It consists of the direct minimization of the nonlinear free-energy function subject to certain linear constraints instead of the usual nonlinear equilibirum equations that express the mass-action laws. Mathematically, the free energy $F(X)$ of a mixture of n chemical species relative to some standard state containing x_j moles of the j-th species can be expressed as

$$F(X) = \sum_{j=1}^{n} x_j \bar{F}_j , \qquad (1)$$

where $X = (x_1, x_2, \ldots, x_n)$ is the set of mole numbers, $\bar{F}_j$ represents the free energy per mole of the j-th species at the given temperature and concentration, $x_j / \bar{x}$; these are defined by

$$\bar{F}_j = RT\left(c_j + \ln \frac{x_j}{\bar{x}}\right), \qquad (2)$$

$$\bar{x} = \sum_1^n x_j, \qquad (3)$$

$$c_j = \frac{\bar{F}_j^o}{RT} + \ln P, \qquad (4)$$

P = pressure in atmospheres,

T = absolute temperature Kelvin,

R = the gas constant,

$\bar{F}_j^o$ = free energy per mole of the j–th species in its standard state.

(For species in liquid state, the pressure term ln P defining c_j is omitted for P's near atmospheric; and for pure species in the solid state, both this term and the term $\ln(x_j/\bar{x})$ are dropped.)

Where there are several compartments instead of one, as in the model, it is necessary to modify the free–energy equation so that concentration is defined separately for each compartment. The necessary change in $F(X)$ is shown in the foregoing formulation of the mathematical problem for Model I.

Real gases and solutions do not conform, over the entire range of composition and of pressure, to the ideal situation described by these equations. To retain the advantages of the simple form of the equations, it has been expedient to define a thermodynamic function called <u>activity</u>, a_j, which is proportional to concentration in mole fraction:

$$a_j = \gamma_j \frac{x_j}{\bar{x}}$$

The constant of proportionality, γ_j, called the activity coefficient, approaches 1 as $x_j/\bar{x}$ tends to 0. In this discussion, mole fraction $x_j/\bar{x}$ is used instead of activity a_j, with the understanding that an approximation is thereby introduced. The use of mole fraction instead of activity in the present model with the very dilute solutions and low pressure involved does not appear to introduce serious error.

The free-energy function is thus defined, once the numerical values of the c_j are determined for the various species. In the case of complex mixtures of gases, extensive tables are available (see, e.g., Ref. 8) containing the free energy values $F_j^\circ/(RT)$ for a large number of chemical species and over a large temperature range. Unfortunately, these data do not include the values for many of the chemical species present in physiological systems. There are, however, equilibrium constants available in the literature for most of the important reactions occurring in the external respiratory system.

Appendix A describes in detail the conversion of the equilibrium constants to the c_j values shown in Table 1. Whenever possible, data were drawn from basic physical chemical tables rather than physiological sources to ensure their applicability under various conditions deviating from those of normal individuals.

THE MASS-BALANCE AND CHARGE CONSTRAINTS

The determination of the equilibrium composition is equivalent to finding the nonnegative set of values x_j that minimizes F(X) as defined by (1) above subject to several sets of linear constraints. The first of these are the mass-balance constraints,

$$\sum_{j=1}^{n} a_{ij} x_j = b_i \qquad (i = 1, 2, \ldots, m), \qquad (5)$$

where there are m different types of "elements"; a_{ij} indicates the number of units of element i in a molecular species j, and b_i is the total number of element weights of element i present in the original inputs. The values of the a_{ij} are the entries in the column below each species in Table 1. Chemically this is equivalent to stating that the mass of the numerous chemical species must be in balance with those of the inputs. For example, the first mass-balance equation can be obtained from Table 1 by multiplying the unknowns x_j by the corresponding entries in the "O_2" row to yield

$$a_1 + v_1 = b_1 = x_1 + x_5 + x_{17} + x_{29} .$$

In addition to the mass-balance constraints of the model, there is one expressed by the "charge" row, which indicates the conservation of electrical charge. It is necessary to introduce this into the model to account for the remarkable ion-selective characteristics of the membrane separating the plasma and red cells. The formulation of this set of

constraints implies the Gibbs–Donnan equilibrium that occurs with such ion–selective membranes; it also provides for the so–called "chloride shift" that occurs through this membrane. This constraint may be formulated in the present context as

$$\sum_{II} z_j x_j = 0, \qquad (6)$$

where z_j, the constant appearing in the charge row, is the net number of positive or negative charges present per unit of the charged species. The summation extends over all species in Compartment II.

In the operations of the model so far, the assumption has been made that there is no net charge difference in the input venous blood, and the charged input "elements" were carefully balanced in accordance with this assumption. If, as is shown in Table 1, one of the compartments with ions contains the constraint that all charges in the compartment sum to zero, and if the input charges sum to zero, it is easy to show that the mass–balance equations imply the electrical neutrality of the other two compartments. Since the first compartment contains only electrically neutral species, (6) implies that all compartments are electrically neutral. Besides providing for the representation of the Gibbs–Donnan equilibrium across the cell membrane and the resulting chloride shift, the charge equation could be used as a means for forcing other compositional changes between compartments when the charge difference is not zero.

Some judgment entered into the choice of the appropriate input "elements" and possible product species present in blood. As for the latter, these were selected to yield a fair representation of the important chemical phenomena that have been observed in the external respiratory system. Experience has shown that the model illustrated in Table 1 is about the smallest matrix in terms of rows, columns, and compartments required to represent these more important phenomena.

There are also many possible choices of "elements" to be used to form the molecular species. The one selected here happens to be minimum in number (notice that there are the same number of vectorally independent columns as there are restricting equations). The selection was also made so that there was a physical interpretation, in terms of nonoverlapping groups of atoms, that permitted obvious simple whole-number combinations to form the various species.

V. SOLUTIONS ON THE DIGITAL COMPUTER AND SIMULATION ON THE ANALOG COMPUTER

DIGITAL-COMPUTER SOLUTIONS

To solve actual numerical cases, the general one-compartment (one-phase) chemical-equilibrium code developed at RAND for the method described in Ref. 5 was extended to cover the multicompartment case. The method is iterative and starts with an arbitrary composition of chemical species satisfying the mass-balance constraints. By means of the assumed chemical composition, a quadratic fit is made to the free-energy function, which is then minimized. This produces a new chemical composition that also satisfies the constraints but has a lower free energy. The process is then iterated. The method is extremely efficient and for this reason has come into wide use for solving chemical-equilibrium problems.

Model I (which has 11 mass-balance equations and 30 chemical species) can be computed on the IBM 704 to four significant figures in approximately one minute with less than 20 iterations. The cost of computing the output composition for a given set of inputs from venous blood and air composition is about $5.00. The currently used digital code is capable of handling systems consisting of 10 times the number of equations and variables. However, systems of such size may require a prohibitive number of iterations before an accurate

solution can be achieved. On the other hand, systems of two to three times the present size are believed to be economically feasible. So far as the authors know, the solution carried out to validate the model (see Sec. VI) represents the largest simultaneous, multiphase chemical system ever solved for equilibrium.

For Model I, the code used only 5,000 of the 32,000 words of high-speed memory space available (including space for about 4,000 words for the code instructions and for about 1,000 words for the problem data, namely, the input values b_i, the energy constants c_j, etc). In addition, the machine has magnetic-tape and drum memories. Thus it is feasible to consider having several human-subsystem models within the machine at the same time; these can be cyclically solved so as to feed input information to each other. For example, a respiratory model at the tissue level could interact with the present external respiratory model. (A simple blood-flow simulation would be needed to interconnect the two subsystems.) This two-subsystem model should give a fairly complete simulation of the full respiratory function of the human body. One immediate application might be to the study of body reactions when breathing in confined atmospheres such as are envisioned for space travel.

ANALOG-COMPUTER SIMULATION

In addition to obtaining accurate numerical values using a digital computer, the authors explored the idea of simulating the respiratory function (so far, just the chemical-equilibrium part) on the electronic circuits of an analog computer. For this purpose, the RAND analog computer (TRAC) was used. This is a differential analyzer originally made by the Reeves Instrument Company, but with many modifications. The various elements of the machine integrators (which are potentiometers) were interconnected by means of a wired plug board that constitutes the Model I "program" for the machine to execute. A series of dials can be turned to vary the inputs to the desired amounts, and the circuits of the machine can be scanned to read the values of any desired output species.

Computer solutions of Model I were undertaken with two goals in mind. The first was the obvious necessity of having fast accurate checks on the mathematical model; the second was the desirability of obtaining, in physical hardware, a simulation of the time-dependent system. Although these two goals are not independent, the digital computer, with high accuracy and reasonably fast solution time, was used to compute the equilibrium conditions and to check the mathematical model. The analog computer, with less accuracy, but much faster solution time, can be used eventually, it is believed, to simulate the dynamic aspects of the model. The initial effort to this end was accomplished in the following way.

The analog computer, as its name implies, is singularly well designed for the simulation of complex time-dependent systems. With the advent of mathematical programming methods, it became possible to simulate complex systems for which the basic problem can be stated in terms of the extremization of a given vector — for example, the chemical-equilibrium problem of Model I as stated above. By means of the methods of mathematical programming, an exact model of the equations for Model I was constructed on the analog machine. An important characteristic of this simulation is that the entire system is interconnected and hence interdependent in just the way the hypotheses of the physiological system are interdependent. This means that a change in level of concentration or activity of any chemical species or component is immediately reflected throughout the system.

All the important parameters of the system were made available on the machine for manual or automatic adjustment. Once the model had been constructed on the machine, the input or known parameters were adjusted by means of potentiometers. The machine quickly computed the equilibrium values for the outputs of the chemical model. That is, the model on the machine, with circulating currents, came to an equilibrium in which the current level and voltage were constant, a simulation of the chemical system. The outputs, or equilibrium values, could then be read on voltmeters or appropriate output devices and the comparison made to the physiological

hypothesis. For example, the effect on the amount of water in the red blood cells was studied by varying the amount of salt in the plasma. This was done by continuously changing the setting of the Na^+ and Cl^- input dials. Similarly the effect of acidity on oxygen pickup was studied by varying the H^+ input, etc. It is quite possible that such a simulator with more subsystems would be an excellent training device to give a medical student at the controls a feel for the effect of this or that change on the functioning of the human system.

To make such a system time-dependent in the most elementary way, the input parameters (potentiometers) — which, for example, set the CO_2 concentration in the lung alveolar sacs — were made to vary in a sinusoidal fashion with a frequency comparable to the breathing rate. The entire system oscillated according to the interdependent relations at the same rate. These oscillations may not correspond to nature, of course, because a more complete representation may require, for example, the simulation of the time lag encountered across physiological boundaries, the interconnection of similar simulations of other organs, and a simulation of the respiratory function at cellular level.

The simulation of Model I required approximately 40 computing amplifiers and 70 potentiometers. The small analog computer at The RAND Corporation can be made to simulate a system about twice the size of the present Model I — e.g.,

the full respiratory function. For larger systems, there are machines available outside RAND. It is also possible that, as subsystems become fully validated, special-purpose analog computers could be built for the sole purpose of simulating the particular subsystems.

VI. VALIDATION OF MODEL I

Where possible, the respiratory model used equilibrium constants derived from physical chemical data rather than those derived from laboratory measurements on the biological medium itself. The rationale for this choice is that data of the second type may reflect the presence of other substances and reactions and may be valid only for the normal or measured conditions. On the other hand, the use of basic data of the first type should allow explorations with the model of conditions that are far from normal in respect to temperature, pressure, blood and air composition, etc., because the more basic equilibrium constants can be expressed functionally in terms of these conditions. The important first question to be asked is how well a model constructed in this manner conforms to the actual physiological phenomena.

To validate the model, the problem chosen was to find the equilibrium amounts of each of the species for the inputs shown in Table 2 for an average resting adult male (at 1 atmosphere and 37°C). This was accomplished by minimizing the sum of the individual partial-molal free-energy functions for the species, subject to the linear constraints for the conservation of mass and of charge, using the electronic computer code described in Sec. V. Table 3 lists the calculated values from the model and the observed values reported[9] for average resting individuals. It can be seen that the correspondence of the calculated and observed values is quite close.

Table 2

INPUTS FOR THE RESPIRATION SYSTEM MODEL[a]

"Element"	From Air (moles per 0.031 moles air)	From Mixed-venous Blood (moles per liter)	Total
O_2	$a_1 = 6.4172 \times 10^{-3}$	$v_1 = 6.83 \times 10^{-3}$	$b_1 = 1.33172 \times 10^{-2}$
CO_2	$a_2 = 9.27 \times 10^{-6}$	$v_2 = 2.27 \times 10^{-2}$	$b_2 = 2.279927 \times 10^{-2}$
N_2	$a_3 = 2.44176 \times 10^{-2}$	$v_3 = 4.37 \times 10^{-4}$	$b_3 = 2.46546 \times 10^{-2}$
H^+	$a_4 = 0$	$v_4 = 46.7$	$b_4 = 46.70$
OH^-	$a_5 = 0$	$v_5 = 46.71973$	$b_5 = 46.71973$
Cl^-	$a_6 = 0$	$v_6 = 0.0814$	$b_6 = 0.0814$
Na^+	$a_7 = 0$	$v_7 = 0.08092$	$b_7 = 0.08092$
K^+	$a_8 = 0$	$v_8 = 0.050$	$b_8 = 0.050$
HBl^{-b}	$a_9 = 0$	$v_9 = 3.09 \times 10^{-3}$	$b_9 = 3.09 \times 10^{-3}$
HP_p^{-b}	$a_{10} = 0$	$v_{10} = 3.80 \times 10^{-3}$	$b_{10} = 3.80 \times 10^{-3}$
HP_r^{-b}	$a_{11} = 0$	$v_{11} = 1.19 \times 10^{-2}$	$b_{11} = 1.19 \times 10^{-2}$
Charge z	$a_{12} = 0$	$v_{12} = 0$	$b_{12} = 0$

[a]These data have been taken from Ref. 9; they represent averages for resting adult males.

[b]The symbol Bl denotes 1/4 reduced hemoglobin molecule, mol. wt. 16,500; symbols P_p and P_r represent miscellaneous protein in plasma and red blood cells, respectively.

Table 5

COMPARISON OF VALUES OBTAINED FROM MODEL I AND OBSERVED BLOOD VALUES

Species	Quantity	Value from Model (moles/vol. produced)	Observed Value[a] (moles/vol. existing)
	Compartment I. Air Out		
O_2	$x_1 / \bar{x}$	0.1395	0.1411
CO_2	$x_2 / \bar{x}$	0.0457	0.0429
N_2	$x_3 / \bar{x}$	0.7731	0.7549
H_2O	$x_4 / \bar{x}$	0.0611	0.0611
	Compartment II. Arterial Plasma		
O_2	x_5	$7.[illegible] \times 10^{-}$	$[illegible] \times 10^{-}$
CO_2	x_6	$7.26 \times 10^{-}$	$6.96 \times 10^{-}$
N_2	x_7	$2.2[illegible] \times 10^{-}$	$2.1[illegible] \times 10^{-}$
H^+	x_8	$1.20 \times 10^{-}$	$[illegible].10[illegible] \times 10^{-}$
OH^-	x_9	$[illegible].[illegible] \times 10^{-}$	$[illegible].57[illegible] \times 10^{-}$
Cl^-	x_{10}	$[illegible].80 \times 10^{-}$	$[illegible].7 \times 10^{-}$
Na^+	x_{11}	(8.092×10^{-2})[illegible]	$[illegible].092 \times 10^{-}$
H_2O	x_{12}	[illegible]	[illegible].71

For footnote, see end of Table.

Table — continued

Species	Quantity	Value from Model (moles/vol. produced)	Observed Value[a] (moles/vol. existing)
		Compartment II. Arterial Plasma	
HCO_3^-	x_{13}	1.[illegible] x 10^{-2}	1.[illegible] x 10^{-2}
H_2CO_3	x_{14}	[illegible] x 10^{-21}	Not reported
$CO_3^=$	x_{15}	2.22 x 10^{-}	Not reported
HP_p^-	x_{16}	(8.80 x 10^{-3})[b]	[illegible] x 10^{-}
		Compartment III. Red Cells	
O_2	x_{17}	[illegible] x 10^{-}	[illegible] x 10^{-}
CO_2	x_{18}	[illegible] x 10^{-4}	[illegible] x 10^{-4}
N_2	x_{19}	1.[illegible] x 10^{-}	2.20 x 10^{-4}
H^+	x_{20}	2.08[illegible] x 10^{-8}	2.09[illegible] x 10^{-8}
OH^-	x_{21}	1.[illegible] x 10^{-7}	1.[illegible] x 10^{-7}
Cl^-	x_{22}	2.[illegible] x 10^{-2}	2.[illegible] x 10^{-2}
K^+	x_{23}	(5.0 x 10^{-2})[b]	[illegible].0 x 10^{-2}
H_2O	x_{24}	17.8[illegible]	18.00
HCO_3^-	x_{25}	[illegible].7 x 10^{-3}	[illegible].[illegible]7 x 10^{-}

For footnote[a], see end of Table.

Table 3 - continued

Species	Quantity	Value from Model (moles/vol. produced)	Observed Value[a] (moles/vol. existing)
Compartment III. Red Cells			
H_2CO_3	x_{26}	4.09×10^{-21}	Not reported
$CO_3^=$	x_{27}	5.84×10^{-6}	Not reported
HBl^-	x_{28}	3.107×10^{-4}	3.636×10^{-4}
$HBlO_2^-$	x_{29}	8.78×10^{-3}	8.7264×10^{-3}
HP_r^-	x_{30}	$(1.19 \times 10^{-2})^b$	1.19×10^{-2}
Total moles			
Compartment I		0.0326879	Respiration Quotient
Compartment II		29.021472	$\frac{CO_2 \text{ out}}{O_2 \text{ in}} = 0.86$
Compartment III		17.9401779	
Compartment II + III		46.9616499	Percent hemoglobin saturation = 96.6

[a]The representative values listed in this column were ob[illegible] from Ref. 5, p. 272 and p. 52, where they are reported as being observed a[illegible] except in the case of dissolved blood gases, which are reported as "synt[illegible]zed" and "derived from basic assumptions and factors and constants."

[b]The values in parentheses are "fixed values" in the sense that they can occur only in the compartment indicated and do not explicitly enter into chemical reactions as represented in this model. They should be exactly equal to the values in the third column. Differences in these two sets of values are an indication of the precision inherent in the computational procedure. The values in Compartment I are given in mole fraction to be comparable to the more familiar volume-percent.

Some interesting features of this equilibrium model may be observed by following some of the reactions and solutions in Tables 1, 2, and 3. For example, it is important to observe the respiration quotient (RQ), the moles of CO_2 out divided by the moles of O_2 in. The moles of CO_2 out may be obtained by subtracting the a_2 value for CO_2 input (Table 2) from 0.0326879 times the $x_2/\bar{x}$ value for CO_2 output (Compartment I, Table 3). If a similar subtraction is carried out for O_2, the results give

$$RQ = \frac{0.00177876}{0.0020674} = 0.86,$$

a value well within the range for resting individuals. Similarly, the per cent of hemoglobin saturation, as determined by the model, is the reasonable-appearing value

$$\frac{100\ x_{29}}{x_{28} + x_{29}} = \frac{0.878}{0.00909} = 96.6\ .$$

Inasmuch as the carbamino reaction involving the combination of hemoglobin and CO_2 was not represented in Model I, it was necessary to compensate for this lack of a CO_2 sink in arterial blood by reducing the total venous CO_2 input by a comparable amount. Consequently the v_2 input value indicated is $1 \cdot 10^{-3}$ moles less than the average true value for total CO_2 in venous blood to compensate for the lack of carbamino representation. Even though the carbamino reaction involves a small part (approximately 5 per cent) of the CO_2 carried by the blood, it accounts for a much higher portion

(approximately 30 per cent) of the CO_2 transferred by the blood during the respiratory cycle. A model of the next degree of sophistication must therefore account for this important reaction.* The representation of the amounts of the other gaseous constituents in Compartment I — namely, N_2 and H_2O — appears to be nicely in line with the inputs and with reported values.

In the cases of columns x_5, x_6, x_7, x_{17}, x_{18}, x_{19}, which show the amounts of O_2, CO_2, and N_2 dissolved in plasma and red cells, respectively, it will be noted that there are some rather wide variations between the values calculated by the machine and the observed values. This is most apparent for O_2 and N_2 dissolved in red cells. There is a possibility that the model results may be more nearly correct than the observed values in these cases. Such very small quantities of dissolved gases are difficult to determine in the laboratory. Then, too, it is possible that small amounts of hemoglobin remained in the analytical samples, which combined with oxygen and thereby made the solubility appear to be greater than it is in the complete absence of hemoglobin. Although the number of moles of these dissolved gases is different for plasma and red cells, their mole fractions are identical in both compartments in the machine solution. This is so for all species appearing except

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*For an excellent description of the physiological role of carbamino compounds in blood, see Ref. 7, pp. 87–88.

for those charged species that are influenced by the Gibbs–Donnan equilibrium. It should be noted that the solubility coefficients used in the model are for water, not for plasma and red cells.

It is also interesting to note that the model creates water in the three compartments from the inputs H^+ and OH^- operating through the reaction

$$H^+ + OH^- \rightleftarrows H_2O .$$

The amount of water formed is influenced slightly by the appropriate demands and supplies of H^+ and OH^- by the competing reactions.

The greatest difficulties in connection with the validation of the model arose in connection with the representation of acidity and concentrations of H^+ and OH^-, columns x_8, x_9, x_{20}, and x_{21}, in plasma and red cells. Acidity of blood samples is usually determined by the use of a pH meter and a glass or similar electrode. It is common to see the expression

$$pH \equiv -\log_{10} [H^+] \text{ or } pH \equiv -\log_{10} a_{H^+} .$$

However, in recent years conclusive arguments have been presented, based on both theoretical and practical electrolytic-cell considerations, that pH values are not measures of hydrogen-ion concentration or activity. Rather, pH determinations are a reliable measure of the "acidity" of the unknown solution in relation to an empirical standard solution having

the same general characteristics, including temperature. Conventional pH measurements are of use primarily for control and gross comparison purposes, but are not suitable for thermodynamic calculations or mass-action law use. There are not even really satisfactory methods for approximating $[H^+]$ or $[OH^-]$ from pH values or vice versa.

The problem this presents in the validation of the operation of the model is to determine if the model calculates $[H^+]$ and $[OH^-]$ accurately when the only laboratory measure of these concentrations for comparison are pH values for plasma and red cells. One approximation suggested in the literature[10] is that

$$\text{pH measured} \pm \Delta\text{pH} = -\log_{10} [H^+] ,$$

when $[H^+]$ is determined from

$$K_w = \frac{[H^+]\,[OH^-]}{[H_2O]} ,$$

where K_w is established by other means, such as conductivity measurements. It will be noted that if the reported pH values for plasma and red cells are taken equal to $-\log_{10} [H^+]$, and $-\log_{10} [OH^-]$ is determined by subtraction from log K_w (which is -13.55 at $37^{\circ}C$), then the resulting concentration product does not equal K_w; this indicates that, in blood,

$$\text{pH measured} \neq -\log_{10} [H^+] .$$

However, if one assumes that the acid-base reactions finally involve only the water contained in the plasma and red-cell

material, and if one reduces the given pH values (and calculated $[OH^-]$ values) to correspond to those for which water only is present, then the values so obtained for real blood satisfy the several mass-action relationships quite nicely and compare well with the values calculated by the model and listed in Table 2. This correction was applied to the values of $[H^+]$ and $[OH^-]$ listed as observed values in Table 2 and as approximated from the reported pH measurements.

The treatment of species x_{11}, x_{16}, x_{23}, and x_{30}, sodium ion and proteins in plasma and potassium ion and proteins in red cells, is described in Appendix B. Species x_{17} and x_{24}, HCO_3^- in plasma and in red cells, is, of course, a crucial ion in the blood both for CO_2 transport and for buffering. It is created by the model in Compartments II and III by the reaction

$$CO_2 + OH^- \rightleftarrows HCO_3^-$$

in the face of the demands and supplies of these inputs from competing reactions. Bicarbonate ion is said to hydrolyze (see p. 219 of Ref. 11):

$$HCO_3^- + H_2O \rightleftarrows H_2CO_3 + OH^-;$$

and it can ionize further:

$$HCO_3^- \rightleftarrows CO_3^= + H^+.$$

The combination of these two reactions gives

$$2HCO_3^- + H_2O \rightleftarrows H_2CO_3 + CO_3^= + H^+ + OH^-.$$

Species x_{14}, x_{15}, x_{26}, x_{27} — namely H_2CO_3 and $CO_3^=$ in plasma and red cells — with their appropriate thermodynamic functions, were introduced in the model to explore their effects on concentrations of HCO_3^-, H^+, and OH^-. The effects of HCO_3^- hydrolysis and second-stage ionization on $[HCO_3^-]$ and acidity appear to be minor.

The concentrations of species H_2CO_3 and $CO_3^=$ are not reported in the literature. These species were retained in the model to illustrate the possibilities of using the model for explorations of this sort. In addition, it has been noted that the model is extremely and correctly sensitive and responsive to changes in the inputs or in the environment (e.g., temperature and pressure).

VII. POTENTIALITIES AND LIMITATIONS OF MODEL I

The authors hasten to admit that the model described is deficient in many respects, for it represents but a first attempt to determine the feasibility of programming a complicated physiological system in this manner. Because the interest of this particular study is centered on the equilibrium phenomena of the system's chemical aspects rather than on the physical flow, mixing, etc., several expedients have been used to avoid incorporating a representation of the physical and transient aspects of the entire external respiratory system in the model. For example, the mechanism of breathing with its complex intermittent flow, mixing, and diffusion effects has been avoided for this initial study in several different ways:

1. By making the set of input "elements," a_1, ..., a_5, representative of a large excess volume of air having the observed composition of the gases of the pulmonary alveoli of a normal resting male at sea level. The assumption introduced by this procedure is that the concentration of gases in the alveoli of resting individuals does not change significantly during the breathing cycle.

2. By relating the required incremental input of "fresh" air of atmospheric composition to the increments of gaseous "elements" needed to convert a unit volume of mixed-venous blood to arterial blood. The "fresh air" inputs, a_1, ..., a_5,

per liter of blood may be estimated on this basis when this information is not provided by the source data.

3. By programming the computer to sample the concentrations of O_2 and CO_2 in either the arterial blood or sac air compartments and calculate by a series of iterations the amounts of "fresh" air of given composition required to make these lung or blood values correspond to previously established standards.

All three of these techniques have been used and are satisfactory within their limitations. Method (2) above was used in obtaining the values shown in Tables 2 and 3. These devices avoid the necessity, at this early stage, of combining a physical model of breathing with the present chemical model, which may require the introduction of a number of concepts in addition to those needed for the chemical model.*

Another assumption implicit in the model is that the arterial blood leaving the lungs comes to equilibrium, through the alveolar and capillary walls, with the gases in the alveoli. As noted earlier, realization of this equilibrium situation appears to be closely approximated by resting individuals. Hence, for the one-cycle case used to validate the model (approximately 0.55 liter of arterial plasma plus approximately 0.45 liter of arterial red cells in equilibrium with each other and with approximately 0.033 moles of alveolar gases, all

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*One mathematical representation of the breathing mechanism can be found in Ref. 12.

subject to the mass-balance constraint provided by the "elements" of one liter of mixed-venous blood plus 0.031 moles of alveolar gases), the assumption is made that equilibrium is reached between the solutions within the red cells and the plasma. A comparison of the results obtained from the model with those obtained from laboratory data on blood samples shows that this assumption does not appear to introduce any serious error for resting individuals.

The multistaged ionization of hemoglobin and the other protein-like blood substances is not represented, and the important carbamino reaction is only implicitly represented, in Model I. In Appendix D, an expanded system (Model II) is shown, demonstrating how these factors may be incorporated.

At the present stage, the model is one of instantaneous reaction, with time not explicitly introduced as an independent variable. This means, of course, that the present representation can deal only with features of the respiratory system that are capable of treatment by reversible thermodynamics; however, this limitation still allows many matters of importance and interest to be explored. In general, if the number of relatively slow chemical reactions entering the model is not large, it may be possible to develop a dynamic model by introducing some simple delays in the electrical analog of the

current model.*

It will also be necessary to develop and introduce the feed-back loops by which changes in CO_2 concentration, and possibly hydrogen-ion concentration, influence the ventilation rate and the rate of blood flow through actions on the cardiovascular system. Consideration must also be given to the boundary conditions essential for the continued functioning of the subsystem. One important limit is the maximum osmotic load tolerated by cells. Fortunately, the model is nicely suited to the incorporation of this limit.

In spite of these difficulties, it should be possible, through the use of models of this type, to demonstrate the detailed interactions of the human respiratory system as the external environment changes and as the inputs from related subsystems change (e.g., in metabolism). Changes in total respiratory gas pressure or relative mixtures will be reflected in the model by the appropriate changes in oxyhemoglobin concentration, alkali reserve, blood-flow rate, breathing rate, plasma composition, etc. Because the energetics are an integral part of the model, changes in work load, temperature,

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*In highly dynamic situations, such as when the respiratory system is stressed by exercise, there is good reason to believe that the controlling reactions will be those involving membrane transfers. There are three such transfers in the external respiratory system, involving (1) the alveolar tissue in the lungs, (2) the red-cell membrane, and (3) the body-cell membrane. The introduction of the appropriate kinetic equations for any or all of these three barriers may suffice to explain all the chemical time effects. The remaining reactions occur as homogeneous reactions in dilute solution or in the gas phase and are thus generally very fast compared to membrane-diffusion processes.

and pressure imposed on the human system should be reflected by the appropriate and detailed response within the modeled respiratory system. Changes in fields, either gravitational, electromagnetic, or electrostatic, can also be introduced through the thermodynamics. Abnormal changes in any of the constituents of the respiratory system, as brought about by pathological conditions or by unusual environments, should elicit the appropriate response in the other constituents, including the energetic aspects. Thus an external respiratory submodel after further development should prove most useful for diagnosis and for predicting the possible effects of unusual stresses on the respiratory system without endangering human life.

Appendix A

A REVIEW OF CERTAIN CHEMICAL THERMODYNAMIC CONCEPTS

For the benefit of readers who are not familiar with chemistry, we shall review some of the basic concepts used in our study, especially the relation of the mass-action law to minimum free energy. Suppose a compartment contains various species such as H_2O, OH^-, H^+, CO_2, HCO_3^-, when CO_2 is dissolved in the solution. The amounts of these various constituents depend on the total amounts of water and carbon dioxide originally "dumped" into the compartment, but <u>their relative concentrations to each other satisfy certain conditions that are independent of the input amounts.</u> In general, the <u>concentrations</u> (or <u>activities</u>) of the species at equilibrium have the property that, independent of the input quantities, one or more ratios of products of concentration among them have fixed values. These nonlinear conditions are called <u>mass-action relationships</u>.

For example, if we let $\bar{x}$ denote the total number of molecules in the mixture, so that

$$\bar{x} = x_{H_2O} + x_{OH^-} + x_{H^+} + x_{CO_2} + x_{HCO_3^-},$$

where

x_{H_2O} = the number of non-ionized water molecules,

x_{OH^-} = the number of ions of OH^-, etc.,

and define

$$N_{H_2O} = \frac{x_{H_2O}}{\bar{x}} ,$$

$$N_{OH^-} = \frac{x_{OH^-}}{\bar{x}} , \text{ etc.,}$$

to be the concentrations of these species in the mixture, then the mass-action law states that

$$\frac{N_{H_2O}}{\left(N_{OH^-}\right)\left(N_{H^+}\right)} = K_1 ,$$

where K_1 has a fixed value (at constant temperature and pressure), called the equilibrium constant for the reaction

$$H^+ + OH^- \rightleftarrows H_2O .$$

Even if no CO_2 were present, or if a salt were added to the mixture, this same relationship would hold despite the fact that the individual concentrations forming the above ratios could be changing drastically. Another mass-action relationship that holds among the concentrations, independent of the amounts of inputs, is

$$\frac{\left(N_{HCO_3^-}\right)\left(N_{H^+}\right)}{\left(N_{CO_2}\right)\left(N_{H_2O}\right)} = K_2 ,$$

where K_2 is the equilibrium constant for the reaction

$$CO_2 + H_2O \rightleftarrows HCO_3^- + H^+ .$$

The conventional method for determining the equilibrium composition is to find the values of the five unknowns x_j that satisfy five equations — two of which are nonlinear and are the two mass-action conditions given above, while the remaining three are linear and express the mass balance in relation to the original inputs, for example,

$$x_{H_2O} + x_{OH^-} + x_{HCO_3^-} = \text{input } OH^-,$$

$$x_{H_2O} + x_{H^+} = \text{input } H^+,$$

$$x_{CO_2} + x_{HCO_3^-} = \text{input } CO_2.$$

As noted earlier in this research memorandum, we have found it more convenient to bypass the mass-action relationships by finding the equilibrium composition through direct minimization of the free-energy function, subject only to the mass-balance conditions.

In general, for a chemical reaction represented by

$$\lambda_1 P_1 + \lambda_2 P_2 + \ldots \rightleftarrows \lambda_1' P_1' + \lambda_2' P_1' + \ldots, \quad (7)$$

the corresponding mass-action relationship is

$$K = \frac{\left(N_1'\right)^{\lambda_1'} \left(N_2'\right)^{\lambda_2'} \ldots}{\left(N_1\right)^{\lambda_1} \left(N_2\right)^{\lambda_2} \ldots}, \quad (8)$$

where the P_j are the reactant species; the P_j' are the product species, the λ_j and λ_j' are the corresponding numbers of moles of each species, K is the equilibrium constant, and the

N_j and N_j' are the concentrations of the constituents P_j and P_j'. We may also state the mass-action law in logarithmic form by taking logarithms of both sides; thus,

$$\ln K = \left[\lambda_1' \ln N_1' + \lambda_2' \ln N_2' + \ldots\right] - \left[\lambda \ln N_1 + \lambda_2 \ln N_2 + \ldots\right] . \qquad (9)$$

It is important to note that a chemical-reaction equation, denoted by (7), is simply a relation among the column vectors $\bar{P}_j$ of input elements a_{ij} associated with each species P_j. Thus if we let

$$\bar{P}_j = (a_{1j}, a_{2j}, \ldots, a_{mj}),$$

we have, corresponding to (7),

$$\lambda_1 \bar{P}_1 + \lambda_2 \bar{P}_2 + \ldots = \lambda_1' \bar{P}_1' + \lambda_2' \bar{P}_2' + \ldots . \qquad (10)$$

This is easily seen from an example. Suppose H^+ and OH^- are considered input "elements" forming species H^+, OH^-, and H_2O. We form the tableau

Input Element	Species		
	H^+	OH^-	H_2O
H^+	1	0	1
OH^-	0	1	1

where the entry a_{ij} in row i and column j is the quantity of the input element i found in the species j. It is clear that the chemical reaction

$$H^+ + OH^- \rightleftarrows H_2O$$

is simply a statement about the corresponding column vectors in the tableau, namely

$$\begin{bmatrix}1\\0\end{bmatrix} + \begin{bmatrix}0\\1\end{bmatrix} = \begin{bmatrix}1\\1\end{bmatrix} .$$

We shall now show that the mass-action law holds for the values of x_j that minimize

$$F(X) = \sum_{j=1}^{n} x_j \bar{F}_j , \tag{11}$$

where in particular $\bar{F}_j$ is given by

$$\bar{F}_j = RT \left(c_j + \ln \frac{x_j}{\bar{x}}\right) . \tag{12a}$$

As noted earlier, this expression for $\bar{F}_j$ is essentially an approximation for dilute solutions and ideal gases of the more general expression (12b). <u>It will be assumed unless otherwise stated that</u>

$$\bar{F}_j = RT \left(c_j + \ln a_j\right) , \tag{12b}$$

where each a_j, the "activity," is some function of the concentration $x_j/\bar{x}$; that is to say, a_j (and hence $\bar{F}_j$, <u>the free energy per mole</u> of the j-th constituent) remains unchanged if all quantities x_j are increased proportionally. We now establish the following purely mathematical theorem:

<u>Theorem</u>: <u>If for every</u> j, $\bar{F}_j = \bar{F}_j(x_j/\bar{x})$ <u>is a function of</u> $x_j/\bar{x}$ <u>only, then</u>

$$\frac{\partial F}{\partial x_j} = \bar{F}_j, \qquad j = 1, 2, \ldots, n. \tag{13}$$

Because of (13), $\bar{F}_j$ is commonly called the partial molar free energy of the j-th constituent. To prove this relation, note first that the free energy F(X) is a homogeneous function of degree one in the variables $(x_1, x_2, \ldots, x_n)$, and for any homogeneous functions of degree one it is generally true that

$$F(X) \equiv \sum_{j=1}^{n} x_j \frac{\partial F}{\partial x_j} . \qquad (14)$$

This relationship (14) is known as Euler's theorem for homogeneous forms of the first degree. In words, it says that total free energy can be determined as if $\partial F/\partial x_j$ is the contribution of the j-th constituent per mole.

The foregoing theorem is easy to prove; we shall establish it, as follows: From (12b), the assumed homogeneity of degree zero for $\bar{F}_j$ for all t, we have

$$tF(x_1, x_2, \ldots, x_n) \equiv F(tx_1, tx_2, \ldots, tx_n) .$$

Hence, taking the partial derivative of both sides with respect to t, we obtain

$$F(x_1, x_2, \ldots, x_n) \equiv \sum_{1}^{n} \frac{\partial F(tx_1, tx_2, \ldots, tx_n)}{\partial (tx_j)} x_j .$$

Setting t = 1 yields (14).

To establish (13), we now assume that F(X) is given by (11), where $\bar{F}_j = \bar{F}_j(x_j / \bar{x})$, and take the partial derivative of F(X) with respect to x_j. This yields

$$\frac{\partial F}{\partial x_j} = \bar{F}_j + \sum_{k=1}^{n} x_k \frac{\partial \bar{F}_k}{\partial \bar{x}}, \qquad j = 1, 2, \ldots, n, \quad (14)$$

where we have replaced $\partial \bar{F}_k / \partial x_j$ by $\partial \bar{F}_k / \partial \bar{x}$ since $\partial \bar{x} / \partial x_k = 1$. We now show that the summation term vanishes. Multiplying both sides by x_j and summing on j yields, by relations (13) and (11),

$$0 = (x_1 + x_2 + \ldots + x_n)\left(\sum_{k=1}^{n} x_k \frac{\partial \bar{F}_k}{\partial \bar{x}} \right).$$

Since

$$x_j \geq 0, \text{ and } \sum_{j=1}^{n} x_j > 0,$$

the second factor of the product must vanish and (13) follows from (15).

Having established that $\bar{F}_j = \partial F / \partial x_j$, let us turn to the main problem of minimizing the free-energy function $F(X)$ subject to mass-balance constraints,

$$\phi_i(X) = \sum_{j=1}^{n} a_{i,j} x_j - b_i = 0, \qquad i = 1, 2, \ldots, m. \quad (16)$$

We now review the Lagrange method for minimizing a general function $F(X)$ subject to m general constraints, $\phi_i(X) = 0$, and later specialize the functions ϕ_i. The first step is to assign unknown multipliers π_i to the functions $\phi_i(X)$ and seek the unconstrained minimum of the function

$$G(X) = F(X) - \pi_1 \phi_1(X) - \pi_2 \phi_2(X) \ldots - \pi_m \phi_m(X). \quad (17)$$

If for some choice of π_1, the point $X = X^o$ where the minimum of $G(X)$ occurs happens to satisfy the constraints $\phi_1(X^o) = 0$, then this unconstrained minimum point X^o for $G(X)$ is the constrained minimum point for $F(X)$. To see this, note that

$$\min G(X) = G(X^o) \cdot F(X^o) ,$$

and that for all other X that satisfy $\phi_1(X) = 0$ we have $F(X) \geq F(X^o)$ because

$$F(X) = G(X) \geq \min G(X) = F(X^o) .$$

When $F(X)$ possesses partial derivatives, and assumes its minimum at some interior point of the domain of definition, it can be shown that such multipliers always exist. We now specialize $\phi_1(X)$ to be linear as given by (16). In this case, we may rewrite $G(X)$ by collecting all terms with common x_j, obtaining

$$G(X) = F(X) - \Sigma(\pi \bar{P}_j)\, x_j + \pi b , \qquad (18)$$

where

$$\pi = (\pi_1, \pi_2, \ldots, \pi_m)$$

is a row vector,

$$\bar{P}_j = (a_{1j}, a_{2j}, \ldots, a_{mj})$$

is the column vector of coefficients associated with species j defined earlier, and

$$b = (b_1, b_2, \ldots, b_m)$$

is the column vector of constants. The coefficient of x_j is the constant $\pi \bar{P}_j$ and depends on the choice of π. At an unconstrained minimum of $G(X)$, X satisfies

$$\frac{\partial F}{\partial x_j} - (\pi \bar{P}_j) = 0$$

for any choice of π. Also for any given chemical reaction

(7) we may multiply the corresponding vector relation (10) by π, obtaining

$$\lambda_1(\pi\bar{P}_1) + \lambda_2(\pi\bar{P}_2) + \ldots = \lambda_1'(\pi\bar{P}_1') + \lambda_2'(\pi\bar{P}_2') + \ldots, \quad (19)$$

which holds for any choice of π. Thus substituting $\partial F/\partial x_j = \pi\bar{P}_j$, we have

$$\lambda_1 \frac{\partial F}{\partial x_1} + \lambda_2 \frac{\partial F}{\partial x_2} + \ldots = \lambda_1' \frac{\partial F}{\partial x_1'} + \lambda_2' \frac{\partial F}{\partial x_2'} + \ldots, \quad (20a)$$

which holds for the X that minimizes G(X) for any choice of π. Since F has a special form (11) that satisfies $\partial F/\partial x_j = \bar{F}_j$, we also have, for any such X,

$$\lambda_1 \bar{F}_1 + \lambda_2 \bar{F}_2 + \ldots = \lambda_1' \bar{F}_1' + \lambda_2' \bar{F}_2' + \ldots . \quad (20b)$$

If we further set

$$\bar{F}_j = RT\,(c_j + \ln a_j),$$

then upon substitution, rearranging of terms, and dropping of the common factor RT, we get the relationship

$$(\lambda_1'c_1' + \lambda_2'c_2' + \ldots) - (\lambda_1 c_1 + \lambda_2 c_2 + \ldots)$$
$$= (\lambda_1' \ln a_2' + \lambda_2' \ln a_2' + \ldots) - (\lambda_1 \ln a_1 + \lambda_2 \ln a_2 + \ldots) \quad (20c)$$

for all X that minimize G(X) for any choice of π. In particular, for that π that yields $X = X^o$ satisfying the mass balances $\phi_1(X) = C$ and thereby minimizing the free energy F(X), this same relationship must hold. But this holds even if we start out with a different set of b_1 values since the expression is independent of b_1. If we define ln K to be

$$\ln K = (\lambda_1' c_1' + \lambda_2' c_2' \ldots) - (\lambda_1 c_1 + \lambda_2 c_2 \ldots), \quad (21)$$

then (20c) establishes the mass-action law in logarithmic form and in terms of activities. If the activities are given by $a_j = x_j / \bar{x}$, then this is the same as the mass-action law stated earlier in equation (9). If

$$a_j = \gamma_j \, x_j / \bar{x} ,$$

where γ_j is some constant, this also yields the mass-action law stated earlier with an adjusted value for ln K. In this manner, the c_j values from the free-energy function can be used to define the equilibrium constants. The converse is shown below.

DETERMINING c_j VALUES FROM EQUILIBRIUM CONSTANTS

As was noted in the text, the equilibrium constants for many common reactions are tabulated in physical chemical tables.

We wish to discuss how to adjust the c_j values so that the equilibrium constants are directly applicable to the model; to be precise, we note that for those x that satisfy the mass balances, the expression for F(X) may be replaced by

$$F(X) = \sum_{j=1}^{n} x_j \left(\bar{c}_j + \ln \frac{x_j}{\bar{x}}\right) - \sum_{i=1}^{m} k_i b_i , \quad (22)$$

where the k_i are constants and the $\bar{c}_j$ bear a direct relationship to the equilibrium constants. The numbers k_i were selected so that when multiplied by the i-th mass-balance [illegible]ation and the m equations summed and subtracted from F(X),

m of the new coefficients of the x_j's, denoted $\bar{c}_j$, would vanish. In place of the original function F(X), the function

$$G(X) = \sum_{j=1}^{n} x_j(\bar{c}_j + \ln \frac{x_j}{x}) \qquad (23)$$

was minimized subject to the mass-balance constraints. Since the two functions differ by a constant,

$$\sum_{i=1}^{m} k_i b_i ,$$

the value of $X = X^o$ that minimizes F(X) also minimizes G(X).

Any m of the $\bar{c}_j$ can be made to vanish by suitably choosing the k_i values, provided that the square array of coefficients $|a_{ij}|$ associated with these j is nonsingular, i.e., provided that their determinant $\neq 0$.

For Model I, the $\bar{c}_j$ values associated with species H^+ and OH^- in Compartment II were made among others to vanish,

$$\bar{c}_{H^+} = \bar{c}_{OH^-} = 0.$$

Now the equilibrium constant for water does not depend on whether we use c_j or $\bar{c}_j$ values for its definition in (21), its value being the same since it must yield the same right-hand member of (20c). Hence, for Compartment II species,

$$\ln K_{H_2O} = \bar{c}_{H_2O} - \bar{c}_{H^+} - \bar{c}_{OH^-} = \bar{c}_{H_2O} .$$

In other words, the value of $\bar{c}_{12} = c_{H_2O}$ can be directly obtained from the equilibrium constant for water. In Appendix C, the entire set of n - m remaining $\bar{c}_j$ values is evaluated in this manner from equilibrium constants.

No attempt was made in the construction of Model I to determine the absolute c_j values as defined in terms of $\bar{F}_j^{\circ}$ values. All c_j values shown are the relative $\bar{c}_j$ values as obtained from equilibrium constants.

Appendix B

CONSTRUCTION OF THE MODEL — INPUTS

The theoretical background given in Appendix A makes possible a more detailed description of the construction and operation of the model shown in Table 1. The first block on the left, labeled "Inputs," contains the "elements" from which the molecular species in the three compartments — "Air Out," "Arterial Plasma," and "Red Cells" — are constructed. These input "elements" have the values in moles, b_1, ..., b_{11}, that are present per unit of time in mixed-venous blood,* plus the values in moles of fresh-air gases, a_1, ..., a_5, entering the lung sacs per unit of time. For the validation of the model, one liter of average mixed-venous blood was used as an input, plus $\sim$ 0.031 moles of degraded "fresh" air.**

Inputs b_1, b_2, b_3, a_1, a_2, a_3, are obvious. The input "elements" in rows 4 and 5, H^+ and OH^-, provide a convenient way to form water in the several compartments and serve as a

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*A troublesome data problem arose in attempting to validate the model. Even among normal individuals, the variability of blood composition is great, and in addition it is necessary for validation to have laboratory data for venous and arterial blood on a completely comparable basis. Fortunately for our purpose, the U.S. Air Force has prepared compilations of biological data in this form. The data for inputs and for comparison with outputs were obtained from Refs. 9 and 13.

**As explained elsewhere, the air inputs may also be obtained by using a large amount of air of lung-sac composition or by programming the computer to search for the proper amount of "fresh" air to meet blood or lung criteria.

mass source and sink for the reactions involving H^+ and OH^-, for example,

$$CO_2 + OH^- \rightleftharpoons HCO_3^- .$$

It will be noted that HCO_3^- is not one of the input "elements," although it is an important constituent of blood. The model creates this species, however, through the reaction given above. To provide for this HCO_3^- formation in terms of mass and charge, the input values of H^+ and OH^- are set different by the amount of HCO_3^- that is present in mixed-venous blood. The CO_2 input b_2, which is also involved in production of HCO_3^-, is the total CO_2, including that present in combined form. It is not directly involved, of course, in the charge balance. The mass-difference effects in terms of H^+ and OH^- caused by the slight basicity of the blood is so small, approximately 1×10^{-10} moles, that it does not require separate mass accounting at this stage.

"Elements" Na^+ and K^+, in rows 7 and 8, are introduced at present essentially as fixed values in plasma and red cells, respectively, inasmuch as entries for these species occur only and separately in these two compartments, and are not allowed to migrate in the model. In real life, of course, there is some K^+ in plasma and Na^+ in red cells. There are also other cations in both compartments, as established by the selective screening action of the red-cell membrane. If and when the data may be available, this ion-screening

mechanism of the membrane can be incorporated in the model as a series of chemical equations with their accompanying thermodynamic functions. At the present stage, however, all cations (except H^+) in plasma and red cells are stated in terms of equivalent Na^+ and K^+, respectively.

The "element" in row 9, designated by the shorthand HBl^-, represents the total hemoglobin present in red cells. It is introduced at this stage as moles of one-fourth hemoglobin molecule, molecular weight approximately 16,500 (one O_2, one Fe per unit).[9] The present model does not allow for the hydrogen ionization of hemoglobin. The aggregating techniques suggested by Alberty[14] provide a method for incorporating the multistaged ionization of hemoglobin into the model with the addition of a modest number of columns. Unfortunately, the data provided for the several ionization constants are for horse hemoglobin at 25°C. If similar data for the ionization of human hemoglobin becomes available, it can be incorporated with possibly some improvement in the representation of "acidity." In Model II (see Appendix D), we have followed an approach suggested by Pauling[15] with regard to the ionization of the hemoglobin molecule.

The "elements" in rows 10 and 11, protein in plasma and in red cells (other than hemoglobin), are inserted in the model at this stage in terms of moles of average molecular weight (equivalent moles) to represent the wide range of molecular species of protein that actually occur in the blood.

At a later stage, and when the data permit, these protein species may be introduced separately and their ionization may be represented in the same fashion as suggested for the case of hemoglobin.

As mentioned, row 12 contains the charge equation, which represents the conservation of charge and accounts for the Gibbs–Donnan equilibrium across the red-cell membrane. At present we have taken $b_{12} = 0$, which dictates electrical neutrality among the several compartments. Any charge difference that may occur, as between red cells and plasma, can be accounted for and its influence on relative composition represented by the introduction of the appropriate molal charge-difference value of b_{12}. Charge differences of the order of -16.8 millivolts between red cells and plasma are reported.[13] Charge differences of this magnitude could have a measurable and possibly physiologically significant effect on the composition of plasma and red cells. Exploration of this phenomenon by means of the model remains for the future. With $b_{12} = 0$, the chloride shift* occurs, so that

$$\frac{[Cl^-]_{plasma}}{[HCO_3^-]_{plasma}} = \frac{[Cl^-]_{red\ cells}}{[HCO_3^-]_{red\ cells}},$$

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*It can be shown that this same relation holds if we allow the net charge b_{12} in Compartment II to be variable and assume that the energy required to maintain this charge can be expressed by adding a new term to the free-energy function.

Appendix C

DETERMINATION OF FREE-ENERGY VALUES

So far, we have described the operation of the model in terms of the several compartments, the thermodynamics involved, the inputs, and the mass and charge conservation constraints. We shall now discuss the numerous chemical reactions involved, how they are represented in the model, and how the mass-action or partial-molal free-energy constraint operates (with the others) to yield an equilibrium solution. The mass-action equations describe the formation of the molecular species of columns $x_1, \ldots, x_{30}$ in the three compartments, I: Air Out, II: Arterial Plasma, and III: Red Cells, and relate similar species occurring in more than one compartment.

For example, the entry 1 in column 12, row 4, Compartment II, the entry 1 in the same column, row 5, and the entry c_{12} in the bottom row together express the chemical equation,

$$H^+ + OH^- \rightleftarrows H_2O ,$$

in the mass-action form,

$$\ln \frac{[H^+]_{II}\,[OH^-]_{II}}{[H_2O]_{II}} = c_{12} ,$$

where

$$c_{12} = \ln K_w ,$$

and K_w is the ionization constant for water (on the mole-fraction scale) at 37°C. It was shown previously that

instead of the separate relations

$$[Cl^-]_{plasma} = [Cl^-]_{red\ cells},$$

and

$$[HCO_3^-]_{plasma} = [HCO_3^-]_{red\ cells},$$

which would hold if the charge equation were removed.

The input values of $v_1, \ldots, v_{12}$, $a_1, \ldots, a_5$, and $b_1, \ldots, b_{12}$, for which the equilibrium-solution values $x_1, \ldots, x_{30}$ were obtained, are listed in Table 2 in the text.

constants like c_{12} derived from equilibrium constants may be used in the model with the same results as if the individual $\bar{F}^o/(RT)$ values for each species were obtained from tables and used.

In a manner similar to that described for the water reactions in Appendix A, the other reactions involved are entered in the model. For the same species occurring in both Compartments II and III, the assumption is made that their original energy coefficients c_j (not necessarily $\bar{c}_j$ values) are the same in both compartments. This results, for example, in

$$[O_2]_{II} = [O_2]_{III}.$$

The other reactions and their c_j values are given in Table 4. In this table, the species are shown in square brackets, [ ], indicating concentration in mole fraction. The c_j values were calculated from the K values shown in Table 5, all converted to the mole-fraction scale.

It is important, in applying these data to the model, that the K values from the literature all be converted to the same scale (i.e., molar, molal, or mole fraction). Most K values are reported on the molal scale, some on the molar; and in some cases, unfortunately, the scale is not indicated. All K values were converted to the mole-fraction scale for use in the model. It is also important that the K values are those for the temperature of interest (310.18 Kelvin in the

Table 4

REACTIONS AND FREE ENERGY VALUES[a] FOR MODEL I, 37°C

Column[b]	Mass Action	$c_j = \ln K$
(1)	$\ln [O_2]_{II \text{ or } III} / [O_2]_I$	-10.89
(2)	$\ln [CO_2]_{II \text{ or } III} / [CO_2]_I$	-7.09
(3)	$\ln [N_2]_{II \text{ or } III} / [N_2]_I$	-11.49
(12)(24)	$\ln [H^+]_{II \text{ or } III} [OH^-]_{II \text{ or } III} / [H_2O]_{II \text{ or } III}$	-39.23
(4)	$\ln [H^+]_{II \text{ or } III} [OH^-]_{II \text{ or } III} / [H_2O]_I$	
	$= c_{12} + \ln [H_2O]_{II \text{ or } III} / [H_2O]_I$	-36.44
(13)(25)	$\ln [CO_2]_{II \text{ or } III} [OH^-]_{II \text{ or } III} / [HCO_3^-]_{II \text{ or } III}$	-21.20
(29)	$\ln [O_2]_{III} [HBl^-]_{III} / [HBlO_2^-]_{III}$	
	$= c_1 + \ln [O_2]_I [HBl^-]_{III} / [HBlO_2^-]_{III}$	-16.23
(14)(26)	$\ln [CO_2]_{II \text{ or } III} [H_2O]_{II \text{ or } III} / [H_2CO_3]_{II \text{ or } III}$	0
(15)(27)	$\ln [CO_2]_{II \text{ or } III} [OH^-]_{II \text{ or } III} / [CO_3^=]_{II \text{ or } III} [H^+]_{II \text{ or } III}$	6.25

[a] All c_j values shown are the adjusted $\bar{c}_j$ values referred to in Appendix A.

[b] The values of $c_j = 0$ for columns (5), (6), (7), (8), (9), (10), (11), (16), (17), (18), (19), (20), (21), (22), (23), (28), (30).

Table 5

EQUILIBRIUM CONSTANTS[a]

Column	Equilibrium Constant
(1)	$K = 0.0232$[b]
(2)	$K = 0.5672$[c]
(3)	$K = 0.0127$[b]
(12)(24)	$\log_{10} K = -13.55$[d]
(4)	$\log_{10} K = \log_{10} K_w + \log_{10} [H_2O]_{II \text{ or } III} / [H_2O]$
	$\log_{10} [H_2O]_{II \text{ or } III} / [H_2O]_I = 1.21396$[e]
(13)(25)	$\log_{10} K = \log_{10} K_w - \log_{10} K_{1_{H_2CO_3}}$,
	$\log_{10} K_{1_{H_2CO_3}} = 6.09$[f]
(29)	$\log_{10} K = -7.0486$[g]
(14)(26)	$\log_{10} K = 700$[h]
(15)(27)	$\log_{10} K = \log_{10} [CO_2]_{II} [OH^-]_{II} / [HCO_3^-]_{II} (K_{2_{H_2CO_3}})$,
	$\log_{10} K_{2_{H_2CO_3}} = -10.25$[i]

[a] All K values on the molar or molal scale were converted to the mole fraction scale for calculating c's.

[b] Ref. 3, p. 54.

[c] Ref. 16, p. 1092.

[d] Ref. 17, p. 152.

[e] Ref. 16, p. 1465.

[f] Ref. 9, p. 272.

[g] Ref. 3, p. 64.

[h] Ref. 3, p. 80.

[i] Ref. 16, p. 1198.

model so far), or are converted to the value for $K_{310.18}$ if the necessary thermodynamic data permit. At a later stage, the appropriate thermodynamic functions can be introduced into the model, relating free energy to temperature and pressure, and perhaps to electrical and gravitational fields and to surface effects.

Appendix D

MODEL II — RESPIRATORY MODEL WITH HEMOGLOBIN STRUCTURE

Mention was made in Sec. VII of certain deficiencies in our Model I of the respiratory function. Of those relating to the chemistry of the blood, the most important are the representation of hemoglobin, including the carbamino reaction, and the multistaged ionization of protein and protein-like substances in the plasma and red cells.* An expanded Model II, shown in Table 6, was constructed to demonstrate one of several ways in which the representation of these phenomena might be improved.

In this model, two-staged ionization of proteins is accounted for in both plasma and red cells. The representation of this type of phenomenon could be expanded to any degree of detail desired. In addition to proteins, it might include a wide range of individual molecular species such as amino acids; and it might include other reactions than ionization — e.g., esterification.

In Model II, the more detailed structuring of hemoglobin and its reactions is represented by a separate compartment IV, as if a separate phase were involved. There are distinct advantages to this form of representation for such complex structures and reactions whenever it can be assumed that reactions with different parts of the molecule are operating

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*A number of hypotheses exist in the literature; we have chosen those due to Adair (2), Pauling (15), and Roughton (7), among others, for illustrative purposes only. In cases where there are competing hypotheses, alternative models could be set up and used to see which best predicts the complex observed phenomena.

Table 6

MODEL II OF THE EXTERNAL RESPIRATORY SYSTEM
OUTPUT COMPOSITION BY MOLECULAR SPECIES

Input "Element" (moles)	Source: Air	Source: V. Blood	Total	I: Air Out	II: Plasma	III. Red Cells	IV. Hb Structure
Type				O_2 CO_2 N_2 H_2O	O_2 CO_2 N_2 H^+ OH^- Cl^- Na^+ H_2O HCO_3^- H_2CO_3 $CO_3^=$ HP_p^- $P_p^=$ HHP_p	O_2 CO_2 N_2 H^+ OH^- Cl^- K^+ H_2O HCO_3^- H_2CO_3 $CO_3^=$ HP_r^- $P_r^=$ HHP_r Hb	"A" H^+"A" $^-$ "C" H^+"C" CO_2"C" "B" "B" O_2"B" (a) O_4"B" (a) O_4"B" (b) O_6"B" (b) O_8"B"
				1 2 3 4	5 6 7 8 9 10 11 12 13 14 15 16 17 18	19 20 21 22 23 24 25 26 27 28 29 30 31 32	34 35 36 37 38 39 40 41 42 43 44
O_2	a_1	v_1	b_1	1	1	1	1 2 2 3 4
CO_2	a_2	v_2	b_2	1	1 1 1	1 1 1	1
N_2	a_3	v_3	b_3	1	1	1	
H^+	a_4	v_4	b_4	1	1 1 −1 −1 1	1 1 −1 −1 1	1 1
OH^-	a_4	v_5	b_5	1	1 1 1 1	1 1 1 1	
Cl^-		v_6	b_6		1	1	
Na^+		v_7	b_7		1		
K^+		v_8	b_8			1	
HP_p^-		v_9	b_9		1 1 1		
HP_r^-		v_{10}	b_{10}			1 1 1	
Hb		v_{11}	b_{11}				1
"A"•			0				$-n_1$
"B" ••			0				$-n_2$
"C"•••			0				-6
Charge in II			0		−1 −1 −1 +1 −1 −2 −1 −2		1 1 2 2 3 4
Free Energy Values				c_1 . . c_4	c_5 . . . . . c_{18}	c_{19} . . . . . c_{32} 0	0 $\ln A$ 0 $\ln B'$ 0 $\ln K'$ 0 $\ln \frac{1}{2}$ 2 $\ln \frac{1}{4}$ 4 $\ln c$
							$\ln A - \ln B'$
							← Hb Free Energy Relations →

• "A^-" refers to an acid, nonoxylabile group of hemoglobin.

•• "B" refers to an oxygen-connecting group of a one-fourth hemoglobin molecule.

••• "C^-" refers to an acid, oxylabile group of hemoglobin.

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independently.* Formal compartmentalization is not essential — by a somewhat different arrangement, hemoglobin and its reactions could be incorporated in Compartment III, Red Cells. Columns 34–37 and 39–44 were designated as species of hemoglobin, and as portions of its molecule, to correspond with Adair's hypothesis[3] of four levels of oxidation of the hemoglobin molecule and with Linus Pauling's square-heme-structure hypothesis and techniques for accounting for the variable affinity of oxygen with changes in oxygen concentration and with changes in pH.[15]

Columns 38, 39, and 34 account for the CO_2–carbamino linking with hemoglobin and its relation with oxygen and hydrogen-ion concentration. The mechanisms suggested by Roughton (pp. 86–88 of Ref. 4) have been followed in this representation.

These more detailed reactions of hemoglobin as represented in compartment IV may be described briefly as follows: The six possible molecular arrangements of hemoglobin according to Pauling are here designated as "B", O_2"B", O_4"B_2"(a), O_4"B_2"(b), O_6"B_3", and O_8"B_4" (columns 39–44). For those molecular arrangements (columns 41, 43, 44) where the square oxygen-linked heme groups interact nonsymetrically, the free

---

*Without such a device, it would be necessary to set up separate columns to represent perhaps a million distinct variants of the hemoglobin molecule corresponding to the different ways its more than 100 groups and parts can ionize, or bond with CO_2 or O_2.

energy is decreased algebraically by a factor, RT ln α, for each unbalanced side, where α is an empirical value determined from experimental evidence. Inasmuch as $\Delta F = - RT \ln K'$, where K' is the free-energy change accompanying the addition of oxygen to heme, the "c" values for the model may be obtained from the logarithms of the separate and appropriate α factors for each of the molecular arrangements.

an analogous manner, Pauling suggests that the effects of ges in hydrogen-ion concentration on hemoglobin may be effected by an empirical correction to the K' value. In this case, empirical factors RT ln β and a so-called acid-strength constant, RT ln A, are used to account for the difference in hydrogen-ion dissociation of oxygenated and unoxygenated hemoglobin. These correction factors are determined from experimental evidence. The precise mechanism for doing this is discussed below.

In terms of Model II, columns 34 and 35, "A^-" and H"A", represent the groups of the hemoglobin molecule that can ionize and that are not affected by oxygen bonding. There are n_1 of these hydrogen-bonding groups. The energy constant per group is assumed to be Pauling's ln A. Columns 36 and 37, "C^-" and H"C", represent an additional eight ionizing groups of the hemoglobin molecule near to and affected by oxygen bonding ("oxylabile"). Two acid groups interacting with each heme were postulated by Pauling to obtain satisfactory agreement between the model and experimental results.

Each "oxylabile" group is assumed also to have the energy constant ln A when no oxygen is attached on the heme and ln A – ln β when oxygen is present. Following Roughton, we allow one CO_2 to attach to one of two oxylabile groups if no O_2 is present.

From the empirically determined values for K', α, A, and β from Pauling, it is therefore possible to calculate the values $c_{34} - c_{44}$ for use in Compartment IV of Model II. The mass balance of all the hemoglobin-associated species of Compartment IV is related to total hemoglobin in Compartment III, Red Cells, through column 33 of Red Cells and through the O_2, CO_2, and H^+ coefficient entries of the hemoglobin-associated Input "Elements."

Model II has not been validated; until this is done it cannot be certain that K', α, A, and β values have been correctly interpreted in the model. For example, the energy constants c_j of Model II are on a per-group basis, whereas Pauling's A and β values may apply to the computation of a pair of groups.

Appendix E

SIMULATING THE RESPIRATORY FUNCTION ON AN ANALOG COMPUTER

THE USES OF THE COMPUTERS

Computer solutions of the lung model have been undertaken with two goals in mind. The first is the obvious necessity to make sensitive checks on the mathematical model. A physiological model is necessarily founded on many parameters and a number of hypotheses, both explicit and implicit. The ability to make fast, deliberate tests of these underlying assumptions has aided materially in the validation of this first model.

The second goal is to obtain, in physical hardware, a simulation of the time-dependent system. Such a simulation should present the complex interplay of component chemical reactions; but it should do more. It should be amenable to the analysis of individual reactions as well as the whole; it should, of course, compute the equilibrium conditions; and it should have sufficient capacity and speed to enable an analysis of the transient change from one equilibrium state to another. Such a change in equilibrium conditions will occur, for example, when the lungs are suddenly exposed to pure oxygen instead of the normal air mixture.

Almost any physiological model that approaches reality will be sufficiently complex to obfuscate one's mental image of the system. But the analog-computer system has the

advantage that it may be built up a piece at a time to any desired complexity. Hence, the goals mentioned above seem perfectly feasible, although certain limitations, such as computer size, are apparent. Despite the fact that the two goals overlap, it was decided to attain them on different computers. The digital computer, with high accuracy but relatively long solution time, is used to compute the equilibrium conditions of the system and hence to test the underlying hypothesis of the model. The analog computer, with lower accuracy but much shorter solution time, can be used to search through a range of parameters or can eventually be used, we believe, to simulate the dynamic aspects of the model. For the present, it is a valuable tool for tracing the effects of continuously varying inputs to the system. For example, the analog can be used in complex experimental situations for estimating equilibrium constants by regarding these constants as parameters to be varied continuously on the machine until a good fit is found between observations and predictions.

CONTINUOUS OPTIMIZATION AND THE ANALOG COMPUTER

The problem of continuous optimization, as compared to the static, one-time, optimization of Appendix D, is to compute and display the transient phenomena of a complex system as it changes under the influence of a time-dependent parameter. The central postulate is Hamilton's principle, the principle of least action from classical mechanics.

The system is defined as in the text. The free-energy function $F(X)$ is to be minimized subject to mass-balance and charge constraints. Using the Lagrangian, we write, for k = I, II, III,

$$G(X,\pi) = F(X) - \sum_{i=1}^{m} \pi_i \phi_i = \sum_{j=1}^{n} x_j \left(c_j + \ln \frac{x_j}{\bar{x}_k}\right) - \sum_{i=1}^{m} \pi_i \phi_i(x), \quad (24)$$

where $\phi_i(X) = \sum_{j=1}^{n} a_{ij} x_j - b_i$. At equilibrium, we require

$$\left.\begin{aligned} \frac{\partial G}{\partial x_j} &= c_j + \ln \frac{x_j}{\bar{x}_k} - \sum_{i=1}^{m} a_{ij} \pi_i = 0 \text{ for each } j, \\ \frac{\partial G}{\partial \pi_i} &= \phi_i(X) = 0 \text{ for each } i, \end{aligned}\right\} \quad (25)$$

where the π_i are the Lagrangian multipliers.

A unique solution, or equilibrium condition, obtains on the computer when a set of mole numbers X and a vector π identically satisfy the equations (25).

If the physical system represented by Model I is well behaved, it will exhibit at a solution certain stability properties, and the system will remain stationary until a parameter of the system is redefined, e.g., the quantity of a reactant. At such a time, transient phenomena are exhibited until a new equilibrium obtains. For most parameters of the system, small changes of the parameter reflect small changes in the solution; that is, the solution is a continuous function of the parameters of variation. Thus, if a parameter is

a slowly changing function of time, the solution moves in a trajectory that continuously minimizes $F(X)$. Thus (25) always holds, although $G = G(X,\pi,t)$.

THE TECHNIQUE OF THE ANALOG SOLUTION

Accurate continuous simulation of a chemical complex may be accomplished on an analog computer by means, essentially, of the method of steepest descent. The analog is desirable because of the characteristically short solution time available, particularly in the high-gain mode of computation. The general method is shown in a previous paper, "Continuous Programming Methods on the Analog,"[18] which contains a bibliography. Some modifications have ensued, however, which represent a departure from previous programming methods; some details will accordingly be shown in this Appendix.

The essential justification for the method employed comes from the studies of convergence questions in the literature.[19][20] T. Kose, in a 1956 paper, considered the convergence of a solution of the mathematical programming problem as solved on an analog computer. To use his result, it is necessary to postulate the existence and uniqueness of a solution, considerations which are taken up for more general programming problems elsewhere in the literature of mathematical programming. With these hypotheses, we have the following result.

Theorem. If $G(X,\pi)$ is a strictly concave, differentiable function of X as well as a strictly convex and differentiable function of π for $x_j \geq 0$, then all solutions of the system of of differential equations,

$$\alpha \dot{x}_j = \delta_{x_j} \frac{\partial G}{\partial x_j} ,$$

$$-\alpha \dot{\pi}_i = \delta_{\pi_i} \frac{\partial G}{\partial \pi_i} = \delta_{\pi_i} \phi_i(x) ,$$

$$\delta_{x_j} = \begin{cases} 0 & \text{if } x_j = 0 \text{ and } \frac{\partial G}{\partial x_j} < 0 , \\ 1 & \text{otherwise} , \end{cases}$$

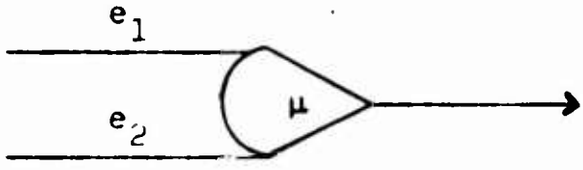
$$\delta_{\pi_i} = \begin{cases} 0 & \text{if } \pi_i = 0 \text{ and } \frac{\partial G}{\partial \pi_i} > 0 , \\ 1 & \text{otherwise} , \end{cases}$$

α = a positive time constant,

necessarily converge to a unique saddle point.

It can be shown that the conditions of the theorem are satisfied by the function G. The constant α is arbitrary and we wish to make it very small so that the solution may be obtained in a short time. Of course, various practical considerations obtain on the analog computer, because the computer is a physical device with characteristics (e.g., frequency limitations) of its own, and these characteristics supervene on the theoretical mathematical statement. With these considerations in mind, we may proceed to program the problem.

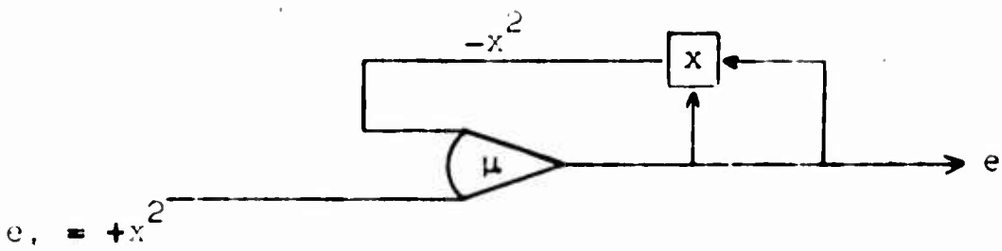
It is required to maintain the relations (25) identically, independent of a new time variable t. To this end, the relations (25) are programmed on amplifiers in the high-gain mode, the outputs of which are the vectors X and π. In order to explain this mode, we start with the basic operational unit of the computer, the high-gain amplifier, represented by the symbol



$$e_0 = -\mu(e_1 + e_2) \qquad (26)$$

where μ is the "gain" of the amplifier and is usually of the order of 10^6. Note the sign change and the addition. Since the output variable, e_0, is limited, for practical electronic reasons, to $\pm$ 100 units, the sum of the inputs is bounded by $\pm\ 10^{-4}$ units; i.e., the sum of the inputs must be very near zero, and we <u>regard this device as a restriction on the inputs</u>.

In order to control the sum of the inputs, the amplifier is normally used with a "negative feedback" loop. The design of this loop defines the mathematical operation of the unit. Thus, just as an example, it is possible to take the (positive) square root of an input, e_1, by inserting a "multiplier" in the feedback:



(27)

A sign change occurs in the multiplier. A heuristic explanation of the operation may be had by regarding the amplifier as an integrator. The output, i.e., the integral, will be steady when the sum of the inputs, i.e., the derivative, is zero. Thus, $\Delta(-x^2 + x^2)$ is a differential operator for e_0, the whole system is a function of time, and as t gets large $\Delta(-x^2 + x^2)$ goes to zero. This system is stable since if e_i is given a positive increment, e_0 takes a negative increment and $-x^2$ decreases bringing the sum of the inputs again to zero. The whole operation should be regarded, now, as determining e_0. If the gain is sufficiently high, say 10^6, the accuracy is very good since small errors in e_0 cause very significant errors in the zero sum of the inputs and in the right direction to correct e_0.

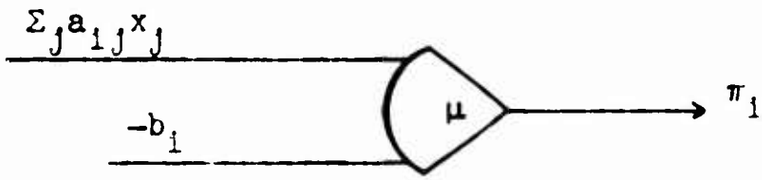
An important thing to note is that e_0 was arbitrarily defined; it has no necessary relation to e_i. But once it is defined, $e_0 = f(e_i)$, it is necessary to construct the inverse function generator, $e_i = f^{-1}(e_0)$, for the feedback loop. Also the feedback loop may itself be implicitly defined.

Using such self-regulating loops, we may instrument the complex equilibrium problem, and the computer will

automatically seek the equilibrium values, i.e., values for which each of the interconnected loops is satisfied. Such a solution requires a few milliseconds. Thus, we instrument the mass-balance equations,

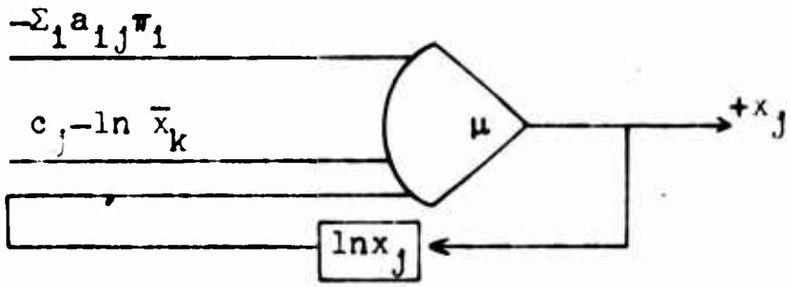
$$\sum_{j=1}^{n} a_{ij}x_j - b_i = 0 ,$$

and name the outputs π_i:



(28)

The first of equations (2) are instrumented and the outputs named $+x_j$:



(29)

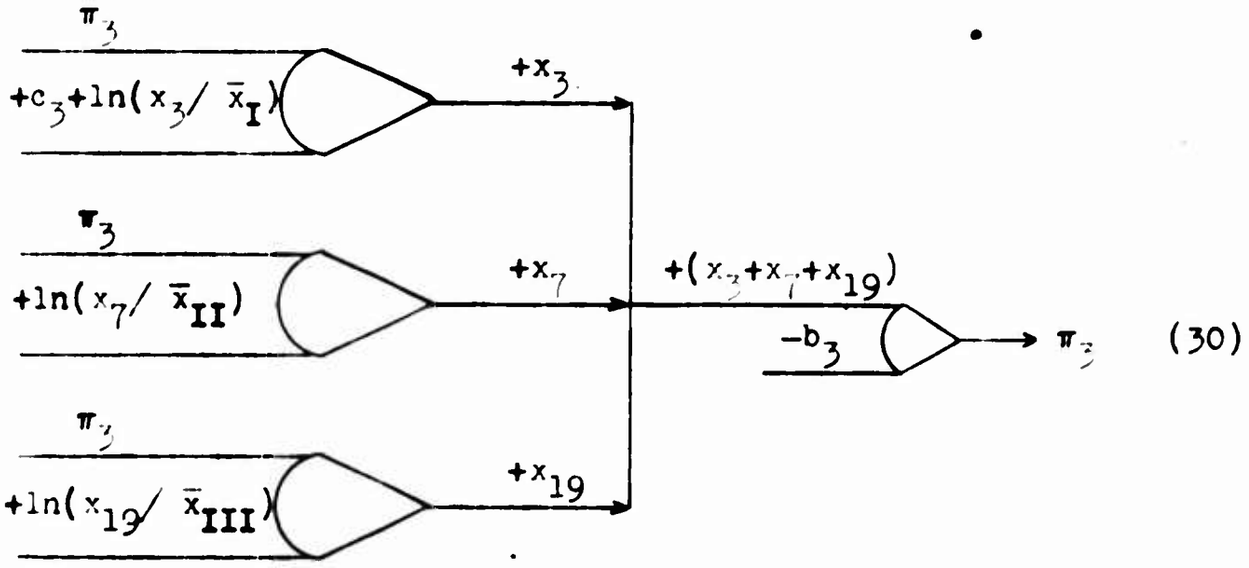
Note that it is necessary to generate $\ln x_j$.

Since the outputs of (28) and (29) are in the inputs of (29) and (28), respectively, it is sufficient to multiply by the appropriate coefficients and interconnect; each is the feedback for the other. The parameters b_i and c_j are available as constants or as functions of time.

As an example of the above discussion, the N_2 (nitrogen) distribution lends itself well since it is interconnected

with the other species only through $\bar{x}_k$, which we may consider constant for the present.

With reference to Model I, the following diagram was constructed:



(30)

The generators for $\ln x_j$ are not shown. The constants c_7 and c_{19} satisfy

$$c_7 = c_{19} = 0,$$

for the reasons given in the text; π_3 automatically takes the proper sign; $c_3 + \ln(x_3/\bar{x}_I)$ is a constant since the concentration of N_2 in alveolar sac air is a postulated constant and c_3 is the tabulated solubility constant for N_2. This closed loop immediately computes the equilibrium x_j and π_3. At equilibrium, the sum of the inputs to each amplifier is zero, as required of amplifiers in the high-gain mode, and hence equation (25) is satisfied. Equations $x_j \geq 0$ may be invoked,

as required, by means of a limiter around the x_j amplifiers. Actually $x_j > 0$, and the limiters function only during the turn-on phase of the computer. Finally,

$$\pi_3 = c_3 + \ln \frac{x_3}{x_I} = \ln \frac{x_7}{x_{II}} = \ln \frac{x_{19}}{x_{III}} ,$$

or (31)

$$\ln \frac{[x_3]}{[x_7]} = c_3 = \ln K ,$$

where the square brackets mean "concentration" and the mass-action law constant is satisfied.

Computation of the $\ln x_j$ is not a straightforward procedure. It is done here by a linear approximation, but obviously more sophisticated techniques could be used. Also, it is sometimes necessary to attenuate a natural high-frequency phenomenon that occurs in high-gain loops. Very small capacitors may be used without affecting the computation.

The basic system requires just **n + m amplifiers**; but because of scale-factor problems, trace elements must be computed from the mass-action constants using multipliers as in White, et al.,[5] or by some other means.

THE CONTINUOUS ANALOG SOLUTION

The simplest continuous solution for the equilibrium problem, when $G = G(x,\pi,t)$, can be illustrated by means of the example given above.

Let

$$b_3 = b_3(t) = A + B \sin wt. \qquad (32)$$

If w is a moderate frequency — say, the breathing rate — then the computation rate of the machine is so high that for any t the instantaneous equilibrium conditions will obtain. The function Q will then oscillate with angular frequency w, a continuous function of $b_3(t)$. Experiments of this sort have been performed.

Of course, each of the parameters is available for manual investigation of its effect on the system. However, the more interesting cases arise when one attempts to define the delay functions, diffusion equations, temperature dependencies, and such complexities as may actually occur. As an example, there is the question of the equilibrium trajectory when the pressure is gradually reduced and then the atmosphere is suddenly switched to pure oxygen. Such a complex question has not been investigated but seems perfectly feasible of solution.

Methods for <u>continuous</u> optimization of a complex system have had a relatively short history in the literature. In general, this problem is related to the synthesis of optimal control systems or, better, the optimal synthesis of optimal control systems. In such a problem, a complex system undergoing transformation is automatically to be optimized with respect to a quality of the output. Ordinarily, then, a feedback link is required to alter one or more inputs, and a criterion is required to measure the performance of the system

with respect to a (an optimal) standard. In particular, see Ref. 21.

The present problem is somewhat simpler than the complete control system, but involves more complex aspects as the physiological model increases in size. For the present, we continuously (in time) compute the equilibrium values of a complex chemical system as the inputs vary at random. Later on, the inputs will be outputs computed from other physiological subsystems, and the whole will be optimized according to viable criteria.

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